

(12) **United States Patent**
Li et al.

(10) **Patent No.:** **US 9,333,297 B2**
(45) **Date of Patent:** ***May 10, 2016**

(54) **DRUG-DELIVERY PUMP WITH INTELLIGENT CONTROL**

(71) Applicants: **Po-Ying Li**, Monrovia, CA (US);
Shengtao Li, La Puente, CA (US);
Jonathan K. Lee, Montebello, CA (US);
Patrick Ryan, Los Angeles, CA (US);
Alice Lai, Pasadena, CA (US); **Sean Caffey**, Pasadena, CA (US); **Mark S. Humayun**, Glendale, CA (US)

(72) Inventors: **Po-Ying Li**, Monrovia, CA (US);
Shengtao Li, La Puente, CA (US);
Jonathan K. Lee, Montebello, CA (US);
Patrick Ryan, Los Angeles, CA (US);
Alice Lai, Pasadena, CA (US); **Sean Caffey**, Pasadena, CA (US); **Mark S. Humayun**, Glendale, CA (US)

(73) Assignee: **MiniPumps, LLC**, Pasadena, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 157 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/035,835**

(22) Filed: **Sep. 24, 2013**

(65) **Prior Publication Data**

US 2014/0094771 A1 Apr. 3, 2014

Related U.S. Application Data

(63) Continuation-in-part of application No. 12/858,808, filed on Aug. 18, 2010, now Pat. No. 9,199,035, which is a continuation-in-part of application No. 12/463,265, filed on May 8, 2009.

(Continued)

(51) **Int. Cl.**
A61M 5/168 (2006.01)
A61M 5/172 (2006.01)

(Continued)

(52) **U.S. Cl.**
CPC **A61M 5/172** (2013.01); **A61M 5/148** (2013.01); **A61M 5/14244** (2013.01);

(Continued)

(58) **Field of Classification Search**
CPC . A61M 5/172; A61M 5/1723; A61M 5/3146;

A61M 2005/1402; A61M 5/14244; A61M 5/14248; A61M 5/14276; A61M 5/16804; A61M 5/16809; A61M 5/16854; A61M 2005/14252; A61M 2205/3341; A61M 2205/3334; A61M 2205/3331; A61M 2205/3368; A61M 2205/50; A61M 2205/0222; A61M 2205/0238; A61M 2205/8206; A61M 2205/8293; A61M 31/002; A61M 2210/0693; A61M 2210/0612; G06F 19/3468

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,445,477 A 7/1948 Folkman
3,175,558 A 3/1965 Caillonette et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CN 1321096 A 11/2001
CN 102576385 A 7/2012

(Continued)

OTHER PUBLICATIONS

Examination Report Received for Mexican Patent App. No. MX/A/2012/012133 mailed on Sep. 25, 2014.

(Continued)

Primary Examiner — Bhisma Mehta

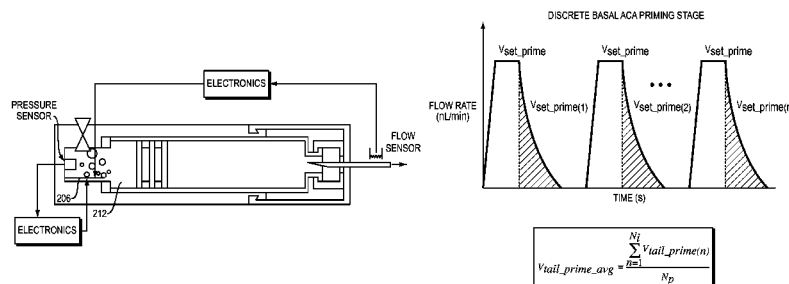
Assistant Examiner — Jenna Zhang

(74) *Attorney, Agent, or Firm* — Morgan, Lewis & Bockius LLP

(57) **ABSTRACT**

Embodiments of the present invention utilize a closed-loop feedback control system to ensure accurate drug delivery. This control system may, for example, utilize a flow sensor to measure the volume of delivery and an intelligent control algorithm to anticipate and compensate for overdoses and underdoses. Feedback control systems in accordance herewith can be applied to any piston- or plunger-driven pump system utilizing sensors that measure flow directly or indirectly. In some embodiments, adjustments are made based on the flow "tail" that occurs in a piston- or plunger-type pump as relaxation of the plunger material continues to push fluid out of the drug reservoir; this residual flow eventually ceases after the plunger returns to its natural state.

14 Claims, 8 Drawing Sheets



Related U.S. Application Data

- (60) Provisional application No. 61/051,422, filed on May 8, 2008, provisional application No. 61/197,751, filed on Oct. 30, 2008, provisional application No. 61/197,769, filed on Oct. 30, 2008, provisional application No. 61/198,131, filed on Nov. 3, 2008, provisional application No. 61/198,090, filed on Nov. 3, 2008, provisional application No. 61/234,742, filed on Aug. 18, 2009, provisional application No. 61/704,946, filed on Sep. 24, 2012.

(51) **Int. Cl.**

A61M 5/31 (2006.01)
A61M 5/142 (2006.01)
A61M 5/148 (2006.01)
G06F 19/00 (2011.01)
A61M 5/155 (2006.01)
A61M 5/145 (2006.01)
A61M 31/00 (2006.01)

(52) **U.S. Cl.**

CPC *A61M 5/14248* (2013.01); *A61M 5/14276* (2013.01); *A61M 5/14526* (2013.01); *A61M 5/16804* (2013.01); *A61M 5/16809* (2013.01); *A61M 5/3146* (2013.01); *G06F 19/3468* (2013.01); *A61M 5/14586* (2013.01); *A61M 5/14593* (2013.01); *A61M 5/155* (2013.01); *A61M 5/16854* (2013.01); *A61M 31/002* (2013.01); *A61M 2005/14204* (2013.01); *A61M 2005/14252* (2013.01); *A61M 2005/14513* (2013.01); *A61M 2205/0222* (2013.01); *A61M 2205/0238* (2013.01); *A61M 2205/3331* (2013.01); *A61M 2205/3334* (2013.01); *A61M 2205/3341* (2013.01); *A61M 2205/3368* (2013.01); *A61M 2205/50* (2013.01); *A61M 2205/8206* (2013.01); *A61M 2205/8231* (2013.01); *A61M 2205/8293* (2013.01); *A61M 2210/0612* (2013.01); *A61M 2210/0693* (2013.01)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,731,681 A 5/1973 Blackshear et al.
 3,760,805 A 9/1973 Higuchi
 3,894,538 A 7/1975 Richter
 3,916,899 A 11/1975 Theeuwes
 3,977,404 A 8/1976 Theeuwes
 4,140,121 A 2/1979 Kuhl et al.
 4,140,122 A 2/1979 Kuhl et al.
 4,150,673 A 4/1979 Watt
 4,164,560 A 8/1979 Folkman et al.
 4,180,375 A 12/1979 Magnussen
 4,203,441 A 5/1980 Theeuwes
 4,237,881 A 12/1980 Beigler et al.
 4,300,554 A 11/1981 Hessberg et al.
 4,373,527 A 2/1983 Fischell
 4,543,088 A 9/1985 Bootman et al.
 4,553,973 A 11/1985 Edgren
 4,692,145 A 9/1987 Weyant
 4,738,657 A 4/1988 Hancock et al.
 4,751,926 A 6/1988 Sasaki
 4,760,837 A 8/1988 Petit
 4,781,675 A 11/1988 White
 4,781,695 A 11/1988 Dalton
 4,838,887 A 6/1989 Idriss
 4,853,224 A 8/1989 Wong
 4,886,499 A 12/1989 Cirelli et al.
 4,886,514 A 12/1989 Maget
 4,888,176 A 12/1989 Langer et al.

4,902,278 A 2/1990 Maget et al.
 4,923,457 A 5/1990 Ellingsen
 4,944,659 A 7/1990 Labbe et al.
 4,959,217 A 9/1990 Sanders et al.
 4,969,874 A 11/1990 Michel et al.
 5,062,834 A 11/1991 Gross et al.
 5,066,276 A 11/1991 Wang
 5,067,491 A 11/1991 Taylor et al.
 5,090,963 A 2/1992 Gross et al.
 5,108,372 A 4/1992 Swenson
 5,135,498 A 8/1992 Kam et al.
 5,135,499 A 8/1992 Tafani et al.
 5,147,647 A 9/1992 Darougar
 5,163,909 A 11/1992 Stewart
 5,164,188 A 11/1992 Wong
 5,171,213 A 12/1992 Price, Jr.
 5,178,604 A 1/1993 Baerveldt et al.
 5,207,227 A 5/1993 Powers
 5,213,568 A 5/1993 Lattin et al.
 5,242,406 A 9/1993 Gross et al.
 5,242,408 A 9/1993 Jhuboo et al.
 5,252,192 A 10/1993 Ludwig
 5,279,607 A 1/1994 Schentag et al.
 5,318,540 A 6/1994 Athayde et al.
 5,318,557 A 6/1994 Gross
 5,354,264 A 10/1994 Bae et al.
 5,368,571 A 11/1994 Horres, Jr.
 5,399,166 A 3/1995 Laing
 5,407,441 A 4/1995 Greenbaum
 5,425,716 A 6/1995 Kawasaki et al.
 5,443,505 A 8/1995 Wong et al.
 5,458,095 A 10/1995 Post et al.
 5,462,739 A 10/1995 Dan et al.
 5,472,436 A 12/1995 Fremstad
 5,474,527 A 12/1995 Bettinger
 5,476,445 A 12/1995 Baerveldt et al.
 5,505,697 A 4/1996 McKinnon et al.
 5,527,288 A 6/1996 Gross et al.
 5,553,741 A 9/1996 Sancioff et al.
 5,616,219 A 4/1997 Patterson
 5,629,008 A 5/1997 Lee
 5,676,651 A 10/1997 Larson, Jr. et al.
 5,697,153 A 12/1997 Saaski et al.
 5,704,520 A 1/1998 Gross
 5,707,499 A 1/1998 Joshi et al.
 5,713,857 A 2/1998 Grimard et al.
 5,725,017 A 3/1998 Elsberry et al.
 5,725,493 A 3/1998 Avery et al.
 5,741,275 A 4/1998 Wyssmann
 5,782,799 A 7/1998 Jacobsen et al.
 5,785,688 A 7/1998 Joshi et al.
 5,788,682 A * 8/1998 Maget A61F 13/00063
 5,798,114 A 8/1998 Elsberry et al.
 5,798,115 A 8/1998 Santerre et al.
 5,800,420 A 9/1998 Gross et al.
 5,824,072 A 10/1998 Wong
 5,830,173 A 11/1998 Avery et al.
 5,836,935 A 11/1998 Ashton et al.
 5,868,697 A 2/1999 Richter et al.
 5,891,097 A 4/1999 Saito et al.
 5,904,144 A 5/1999 Hammang et al.
 5,951,538 A 9/1999 Joshi et al.
 5,989,579 A 11/1999 Darougar et al.
 5,993,374 A 11/1999 Kick
 5,993,414 A 11/1999 Haller
 6,048,328 A 4/2000 Haller et al.
 6,129,696 A 10/2000 Sibalis
 6,144,106 A 11/2000 Bearinger et al.
 6,203,523 B1 3/2001 Haller et al.
 6,240,962 B1 6/2001 Tai et al.
 6,251,090 B1 6/2001 Avery et al.
 6,254,586 B1 7/2001 Mann et al.
 6,264,971 B1 7/2001 Darougar et al.
 6,281,192 B1 8/2001 Leahy et al.
 6,287,295 B1 9/2001 Chen et al.
 6,370,970 B1 4/2002 Hosokawa et al.
 6,375,972 B1 4/2002 Guo et al.
 6,390,791 B1 5/2002 Maillefer et al.

604/290

(56)	References Cited			2005/0214129 A1	9/2005	Greene et al.	
	U.S. PATENT DOCUMENTS			2006/0004330 A1 *	1/2006	Carlisle	A61M 5/1408
							604/246
				2006/0012280 A1	1/2006	Kang et al.	
6,408,878 B2	6/2002	Unger et al.		2006/0014793 A1	1/2006	Nakamura et al.	
6,413,238 B1 *	7/2002	Maget	A61M 5/14526	2006/0047538 A1	3/2006	Condurso et al.	
			604/132	2006/0052666 A1	3/2006	Kumar et al.	
6,416,777 B1	7/2002	Yaacobi		2006/0052768 A1	3/2006	Joshi et al.	
6,458,102 B1	10/2002	Mann et al.		2006/0075016 A1	4/2006	Kanayama et al.	
6,491,684 B1	12/2002	Joshi et al.		2006/0089619 A1	4/2006	Ginggen	
6,520,936 B1	2/2003	Mann		2006/0116641 A1 *	6/2006	Gordon	A61K 9/0004
6,527,744 B1	3/2003	Kriesel et al.					604/141
6,537,268 B1	3/2003	Gibson et al.		2006/0167435 A1	7/2006	Adamis et al.	
6,589,205 B1	7/2003	Meadows		2006/0178655 A1	8/2006	Santini et al.	
6,669,950 B2	12/2003	Yaacobi		2006/0200073 A1	9/2006	Radmer et al.	
6,697,694 B2	2/2004	Mogensen		2006/0200097 A1	9/2006	Humayun et al.	
6,699,394 B2	3/2004	Tai et al.		2006/0258994 A1	11/2006	Avery	
6,713,081 B2	3/2004	Robinson et al.		2006/0259015 A1	11/2006	Steinbach	
6,719,750 B2	4/2004	Varner et al.		2006/0271020 A1	11/2006	Huang et al.	
6,817,252 B2	11/2004	Wiklund et al.		2007/0021735 A1	1/2007	Bhavaraju et al.	
6,852,097 B1	2/2005	Fulton, III		2007/0060870 A1	3/2007	Tolle et al.	
6,852,106 B2	2/2005	Watson et al.		2007/0066939 A1	3/2007	Krulevitch et al.	
6,899,137 B2	5/2005	Unger et al.		2007/0084765 A1	4/2007	Tse	
6,948,918 B2	9/2005	Hansen		2007/0093752 A1	4/2007	Zhao et al.	
6,955,670 B2	10/2005	Martin et al.		2007/0106199 A1	5/2007	Krivoy et al.	
6,973,718 B2	12/2005	Sheppard, Jr. et al.		2007/0106218 A1	5/2007	Yodfat et al.	
7,070,577 B1	7/2006	Haller et al.		2007/0106557 A1	5/2007	Varghese	
7,225,683 B2	6/2007	Harnett et al.		2007/0112328 A1	5/2007	Steinbach et al.	
7,276,050 B2	10/2007	Franklin		2007/0118066 A1	5/2007	Pinchuk et al.	
7,351,303 B2	4/2008	Liu et al.		2007/0173900 A1	7/2007	Siegel et al.	
7,429,258 B2	9/2008	Angel et al.		2007/0191770 A1	8/2007	Moberg et al.	
7,470,267 B2	12/2008	Joshi et al.		2007/0228071 A1 *	10/2007	Kamen	G05D 7/0647
7,517,440 B2	4/2009	Anex et al.					222/52
7,524,304 B2	4/2009	Genosar		2007/0255233 A1	11/2007	Haase	
7,537,590 B2	5/2009	Santini, Jr. et al.		2007/0255235 A1	11/2007	Olsen et al.	
7,544,190 B2	6/2009	Pickup et al.		2007/0255250 A1	11/2007	Moberg et al.	
7,606,615 B2	10/2009	Makower et al.		2007/0255261 A1	11/2007	Haase	
7,766,873 B2	8/2010	Moberg et al.		2007/0269487 A1	11/2007	de Juan et al.	
7,828,771 B2	11/2010	Chiang et al.		2007/0275384 A1	11/2007	Leppert et al.	
7,867,203 B2	1/2011	Rosenberg et al.		2008/0015494 A1	1/2008	Santini et al.	
7,887,508 B2	2/2011	Meng et al.		2008/0022789 A1	1/2008	Okuno et al.	
7,931,643 B2	4/2011	Olsen et al.		2008/0033255 A1	2/2008	Essenpreis et al.	
8,147,447 B2	4/2012	Sundar et al.		2008/0039768 A1	2/2008	Francis	
8,231,609 B2	7/2012	Pang et al.		2008/0039792 A1 *	2/2008	Meng	A61K 9/0024
8,285,328 B2	10/2012	Caffey et al.					604/114
8,585,648 B2	11/2013	Caffey		2008/0097412 A1	4/2008	Shuros et al.	
8,920,376 B2	12/2014	Caffey et al.		2008/0102119 A1	5/2008	Grovender et al.	
8,939,930 B2	1/2015	Li et al.		2008/0119707 A1	5/2008	Stafford	
2002/0016569 A1	2/2002	Critchlow et al.		2008/0125702 A1	5/2008	Blischak et al.	
2002/0026176 A1	2/2002	Varner et al.		2008/0170936 A1	7/2008	Den Toonder et al.	
2002/0040208 A1	4/2002	Flaherty et al.		2008/0181930 A1	7/2008	Rodstrom et al.	
2002/0103412 A1	8/2002	Trimmer		2008/0194053 A1	8/2008	Huang	
2002/0156462 A1	10/2002	Stultz		2008/0234637 A1	9/2008	McConnell et al.	
2002/0188282 A1	12/2002	Greenberg		2008/0243071 A1	10/2008	Quijano et al.	
2003/0014014 A1	1/2003	Nitzan		2008/0269664 A1	10/2008	Trovato et al.	
2003/0014036 A1	1/2003	Varner et al.		2008/0269678 A1 *	10/2008	Rebours	A61M 5/16827
2003/0064088 A1	4/2003	Carvalho et al.					604/118
2003/0069560 A1	4/2003	Adamis et al.		2008/0275384 A1	11/2008	Mastrototaro	
2003/0141618 A1	7/2003	Braithwaite et al.		2008/0312584 A1	12/2008	Montgomery et al.	
2004/0028655 A1	2/2004	Nelson et al.		2009/0028824 A1 *	1/2009	Chiang	A61M 5/14248
2004/0096410 A1	5/2004	Maley et al.					424/85.7
2004/0100528 A1	5/2004	Howkins et al.		2009/0041624 A1	2/2009	Hochmuth et al.	
2004/0106914 A1	6/2004	Coppeta et al.		2009/0112188 A1	4/2009	Santini, Jr. et al.	
2004/0126253 A1	7/2004	Gray et al.		2009/0188576 A1	7/2009	Kang et al.	
2004/0143221 A1	7/2004	Shadduck		2009/0192493 A1	7/2009	Meng et al.	
2004/0175410 A1	9/2004	Ashton et al.		2009/0205399 A1	8/2009	Sun et al.	
2004/0188648 A1	9/2004	Xie et al.		2009/0227855 A1	9/2009	Hill et al.	
2004/0199130 A1	10/2004	Chornenky et al.		2009/0234366 A1	9/2009	Tsai et al.	
2004/0208910 A1	10/2004	Ashton et al.		2009/0234594 A1	9/2009	Carlisle et al.	
2004/0228734 A1	11/2004	Jeon et al.		2009/0240215 A1	9/2009	Humayun et al.	
2005/0010175 A1	1/2005	Beedon et al.		2009/0259176 A1	10/2009	Yairi	
2005/0065500 A1	3/2005	Couvillon et al.		2009/0281528 A1	11/2009	Grovender et al.	
2005/0076242 A1	4/2005	Breuer		2009/0306585 A1	12/2009	Pang et al.	
2005/0096707 A1	5/2005	Hill et al.		2009/0306594 A1	12/2009	Pang et al.	
2005/0106225 A1	5/2005	Massengale et al.		2009/0306595 A1	12/2009	Shih et al.	
2005/0175708 A1	8/2005	Carrasquillo et al.		2009/0306633 A1	12/2009	Trovato et al.	
2005/0187515 A1	8/2005	Varrichio et al.		2009/0308752 A1	12/2009	Evans et al.	
2005/0208103 A1	9/2005	Adamis et al.		2009/0311133 A1	12/2009	Pang et al.	
2005/0209562 A1	9/2005	Kim		2009/0312742 A1	12/2009	Pang et al.	

(56)

References Cited**U.S. PATENT DOCUMENTS**

2010/0004639	A1	1/2010	Pang et al.
2010/0030550	A1	2/2010	Travieso et al.
2010/0049120	A1	2/2010	Dijkman et al.
2010/0101670	A1	4/2010	Juncker et al.
2010/0114002	A1	5/2010	O'Mahony et al.
2010/0143448	A1	6/2010	Nisato et al.
2010/0222769	A1	9/2010	Meng et al.
2010/0234805	A1	9/2010	Kaufmann et al.
2010/0241103	A1	9/2010	Kraft et al.
2010/0292557	A1*	11/2010	Pesach A61B 5/14532 600/365
2010/0292635	A1	11/2010	Sundar
2010/0305550	A1	12/2010	Meng et al.
2011/0144586	A1	6/2011	Michaud et al.
2011/0184342	A1	7/2011	Pesach et al.
2011/0190702	A1	8/2011	Stumber
2011/0202032	A1	8/2011	Shih et al.
2011/0270188	A1	11/2011	Caffey et al.
2011/0275410	A1	11/2011	Caffey et al.
2011/0275987	A1	11/2011	Caffey et al.
2012/0041427	A1	2/2012	Caffey et al.
2012/0046651	A1	2/2012	Beyer et al.
2012/0222488	A1	9/2012	Slocum
2012/0283691	A1	11/2012	Barnes et al.
2013/0178792	A1	7/2013	Li et al.
2013/0178826	A1	7/2013	Li et al.
2013/0184640	A1	7/2013	Li et al.
2013/0184641	A1	7/2013	Li
2013/0276974	A1	10/2013	Pang et al.
2013/0289497	A1	10/2013	Humayun et al.
2013/0296810	A1	11/2013	Humayun et al.
2014/0074058	A1	3/2014	Shih et al.
2014/0088554	A1	3/2014	Li et al.
2014/0088555	A1	3/2014	Li et al.
2014/0094770	A1	4/2014	Li et al.

FOREIGN PATENT DOCUMENTS

CN	103108665	A	5/2013
CN	102202719	B	11/2014
CN	104353150	A	2/2015
DE	3915708	A1	2/1990
DE	4436540	A1	4/1996
DE	102004036358	A1	2/2006
EP	209677	A1	1/1987
EP	251680	A2	1/1988
EP	646381	A1	4/1995
EP	815896	A2	1/1998
EP	1649884	A1	4/2006
EP	1841491	A1	10/2007
EP	2467797	A1	6/2012
EP	2560703	A2	2/2013
EP	2780055	A2	9/2014
EP	2320989	B1	3/2015
GB	1345764	A	2/1974
GB	1452104	A	10/1976
IE	38474	B1	3/1978
JP	2003-299732	A	10/2003
JP	2015-502785	A	1/2015
WO	84/01718	A1	5/1984
WO	86/07269	A1	12/1986
WO	95/13838	A1	5/1995
WO	96/41159	A1	12/1996
WO	99/17749	A1	4/1999
WO	99/38552	A1	8/1999
WO	99/62576	A1	12/1999
WO	00/26367	A2	5/2000
WO	00/40089	A1	7/2000
WO	00/72900	A1	12/2000
WO	00/74751	A1	12/2000
WO	01/12158	A1	2/2001
WO	01/21234	A1	3/2001
WO	01/26706	A2	4/2001
WO	01/56634	A1	8/2001

WO	01/66173	A1	9/2001
WO	01/94784	A1	12/2001
WO	02/40083	A2	5/2002
WO	02/067688	A1	9/2002
WO	03/002170	A2	1/2003
WO	03/009774	A2	2/2003
WO	03/024360	A1	3/2003
WO	03/072193	A1	9/2003
WO	03/090509	A2	11/2003
WO	2004/002878	A2	1/2004
WO	2004/014969	A1	2/2004
WO	2004/026281	A2	4/2004
WO	2004/066871	A2	8/2004
WO	2004/067066	A1	8/2004
WO	2004/073551	A2	9/2004
WO	2005/034814	A1	4/2005
WO	2005/046769	A2	5/2005
WO	2006/012280	A1	2/2006
WO	2006/014793	A1	2/2006
WO	2006/026768	A1	3/2006
WO	2006/060586	A1	6/2006
WO	2006/075016	A1	7/2006
WO	2006/121921	A2	11/2006
WO	2007/035621	A1	3/2007
WO	2007/065944	A1	6/2007
WO	2007/084765	A2	7/2007
WO	2007/106557	A2	9/2007
WO	2007/112328	A2	10/2007
WO	2007/125456	A2	11/2007
WO	2007/138590	A2	12/2007
WO	2008/024808	A2	2/2008
WO	2008/054788	A2	5/2008
WO	2008/139460	A2	11/2008
WO	2008/151667	A1	12/2008
WO	2009/015389	A2	1/2009
WO	2009/048144	A1	4/2009
WO	2009/086112	A2	7/2009
WO	2009/137780	A2	11/2009
WO	2011/022484	A1	2/2011
WO	2011/025913	A1	3/2011
WO	2011/028997	A1	3/2011
WO	2011/133724	A2	10/2011
WO	2011/133724	A3	1/2012
WO	2013/075109	A2	5/2013
WO	2013/075109	A9	7/2013
WO	2013/075109	A3	10/2013
WO	2014/047638	A1	3/2014
WO	2014/047657	A2	3/2014
WO	2014/047657	A3	7/2014
WO	2015/048093	A2	4/2015

OTHER PUBLICATIONS

PCT International Patent Application No. PCT/US2013/061443, International Preliminary Report on Patentability issued Mar. 24, 2015, 9 pages.

PCT International Patent Application No. PCT/US2013/061494, International Preliminary Report on Patentability issued Mar. 24, 2015, 13 pages.

PCT International Patent Application No. PCT/US2014/057158, International Search Report and Written Opinion mailed Mar. 30, 2015, 14 pages.

Examination Report Received for European Patent Application No. 10760475.3, mailed on Apr. 7, 2015, 7 pages.

Examination Report in European Patent Application No. 07753177.0, mailed on Jan. 29, 2009, 6 pages.

Examination Report in European Patent Application No. 07753177.0, mailed on Feb. 5, 2010, 3 pages.

Extended Search Report issued for European Patent Application No. 11153615.7, mailed on Dec. 15, 2011, 8 pages.

Examination Report in European Patent Application No. 11153618.1, mailed on Oct. 14, 2013, 5 pages.

Extended Search Report issued for European Patent Application No. 11153618.1, mailed on Dec. 12, 2011, 9 pages.

Extended Search Report issued for European Patent Application No. 13168508.3, mailed on Oct. 24, 2013, 7 pages.

(56)

References Cited**OTHER PUBLICATIONS**

Office Action mailed on Apr. 9, 2013 for Japanese Patent Application No. 2010-539873, English translation of "Notification of Reason for Rejection", 6 pages.

Examination Report in Mexican Patent Application No. MX/a/2008/011714, mailed on Jan. 19, 2012.

Examination Report in Mexican Patent Application No. MX/A/2010/012213, mailed on Jan. 16, 2014.

International Application Serial No. PCT/US2007/006530, International Search Report and Written Opinion mailed on Nov. 12, 2007, 15 pages.

International Application Serial No. PCT/US2007/006530, Invitation to Pay Additional Fees and Partial International Search mailed on Jul. 31, 2007, 7 pages.

International Application Serial No. PCT/US2008/087690, International Search Report and Written Opinion mailed on Aug. 11, 2009, 15 pages.

International Application Serial No. PCT/US2008/087690, Invitation to Pay Additional Fees and Partial International Search mailed on May 15, 2009, 5 pages.

International Application Serial No. PCT/US2009/030019, International Search Report and Written Opinion mailed on Jul. 20, 2009, 16 pages.

International Application Serial No. PCT/US2009/030019, Invitation to Pay Additional Fees and Partial International Search mailed on Jun. 5, 2009, 5 pages.

International Application Serial No. PCT/US2009/043313, International Search Report and Written Opinion mailed on Feb. 25, 2010, 16 pages.

International Application Serial No. PCT/US2009/043313, Invitation to Pay Additional Fees and Partial International Search mailed on Nov. 16, 2009, 6 pages.

International Application Serial No. PCT/US2009/043317, International Search Report and Written Opinion mailed on Feb. 16, 2010, 15 pages.

International Application Serial No. PCT/US2009/043317, Invitation to Pay Additional Fees and Partial International Search, mailed on Nov. 16, 2009, 5 pages.

International Application Serial No. PCT/US2009/043325, International Search Report and Written Opinion mailed on Nov. 12, 2009, 18 pages.

International Application Serial No. PCT/US2010/045897, International Search Report and Written Opinion mailed on Dec. 28, 2010, 12 pages.

International Application Serial No. PCT/US2010/047811, Invitation to Pay Additional Fees and Partial Search Report mailed on Dec. 2, 2010, 8 pages.

International Application Serial No. PCT/US2011/033329, International Search Report and Written Opinion mailed Nov. 23, 2011, 16 pages.

International Application Serial No. PCT/US2011/033329, Invitation to Pay Additional Fees and Partial Search Report, mailed Aug. 4, 2011, 5 pages.

International Application Serial No. PCT/US2011/044508, International Search Report and Written Opinion mailed Dec. 1, 2011, 11 pages.

International Application Serial No. PCT/US2013/061494, Invitation to Pay Additional Fees and Partial Search Report, mailed Jan. 28, 2014, 6 pages.

"Krupin Eye Valve with Scleral Buckle, Krupin Eye Valve With Disk", Hood Laboratories Catalogue, F 079 Rev., Nov. 1992, 4 pages.

"The Optimized Advantage—Glaucoma Pressure Regulator", Optimized Advertising Brochure, Journal of Glaucoma, vol. 2, No. 3, 1993, 4 pages.

Chen et al., "Floating-Disk Parylene Micro Check Valve", Micro Electro Mechanical Systems, MEMS, IEEE 20th International Conference, Jan. 21-25, 2007, pp. 453-456.

Chen et al., "Floating-Disk Parylene Microvalve for Self-Regulating Biomedical Flow Controls", Micro Electro Mechanical Systems, MEMS, IEEE 21st International Conference., Jan. 13-17, 2008, pp. 575-578.

Chen et al., "Surface-Micromachined Parylene Dual Valves for On-Chip Unpowered Microflow Regulation", Journal of Microelectromechanical Systems, vol. 16, No. 2, Apr. 2007, pp. 223-231.

Choudhri et al., "A Comparison of Dorzolamide-Timolol Combination Versus the Concomitant Drugs", American Journal of Ophthalmology, vol. 130, No. 6, Dec. 2000, pp. 832-833.

Durham, N.C., "FDA Approves an Industry First!—The MED-EL Cochlear Implant System is FDA Approved for Use With Magnetic Resonance Imaging (MRI)", PR Newswire, Jun. 18, 2003, 3 pages.

Eliason et al., "An Ocular Perfusion System", Investigate Ophthalmology Visual Science, vol. 19, No. 1, Jan. 1980, pp. 102-105.

Hashizoe et al., "Scleral Plug of Biodegradable Polymers for Controlled Drug Release in the Vitreous", Arch Ophthalmology, vol. 112, No. 10, Oct. 1994, pp. 1380-1384.

Jabs, Douglas A., "Treatment of Cytomegalovirus Retinitis—1992", Arch Ophthalmology, vol. 110, No. 2, Feb. 1992, pp. 185-187.

Khoury et al., "Use of Fixed-Dose Combination Drugs for the Treatment of Glaucoma", Drugs & Aging, vol. 24, No. 12, Dec. 2007, pp. 1007-1016.

Kimura et al., "A New Vitreal Drug Delivery System Using an Implantable Biodegradable Polymeric Device", Investigative Ophthalmology & Visual Science, vol. 35, No. 6, May 1994, pp. 2815-2819.

Lo et al., "A Refillable Polymer Drug Delivery Device for Treatment of Ocular Diseases", The Royal Society of Chemistry, Jan. 1, 2007, 28 pages.

Michelson et al., "Experimental Endophthalmitis Treated With an Implantable Osmotic Minipump", Arch. Ophthalmology, vol. 97, Jul. 1979, pp. 1345-1346.

Miki et al., "A Method for Chronic Drug Infusion Into the Eye", Japanese Journal of Ophthalmology, vol. 28, No. 2, 1984, pp. 140-146.

Pincus et al., "Why are Only 50% of Courses of Anti-Tumor Necrosis Factor Agents Continued for Only 2 Years in Some Settings? Need for Longterm Observations in Standard Care to Compliment Clinical Trials", Journal of Rheumatology, vol. 33, No. 12, Dec. 2006, pp. 2372-2375.

Pope et al., "MRI in Patients with High-Grade Gliomas Treated with Bevacizumab and Chemotherapy", Neurology, vol. 66, No. 8, Apr. 2006, pp. 1258-1260.

Rubsamen et al., "Prevention of Experimental Proliferative Vitreoretinopathy With a Biodegradable Intravitreal Implant for the Sustained Release of Fluorouracil", Arch. Ophthalmology, vol. 112, No. 3, Mar. 1994, pp. 407-413.

Sanborn et al., "Sustained-Release Ganciclovir Therapy for Treatment of Cytomegalovirus Retinitis", Arch Ophthalmology, vol. 110, No. 2, Feb. 1992, pp. 188-195.

Smith et al., "Intravitreal Sustained-Release Ganciclovir", Arch Ophthalmology, vol. 110, No. 2, Feb. 1992, pp. 255-258.

Stark-Vance, "Bevacizumab and CPT-11 in the Treatment of Relapsed Malignant Glioma", Neuro Oncology, vol. 7, No. 3, Abstract from the World Federation of Neuro-Oncology Second Quadrennial Meeting and Sixth Meeting of the European Association for Neuro-Oncology, May 5-8, 2005, Abstract 342, Jul. 2005, p. 369.

Steyer, Robert, "Alcon Eye-Drug Setback Raises the Stakes", Available online at <<http://www.thestreet.com/story/10187873/1/alcon-eye-drug-setback-raises-the-stakes.html>>, Oct. 14, 2004, 4 pages.

Strohmaier et al., "The Efficacy and Safety of the Dorzolamide-Timolol Combination Versus the Concomitant Administration of its Components", Ophthalmology, vol. 105, No. 10, Oct. 1998, pp. 1936-1944.

Xie et al., "An Electrochemical Pumping System for On-Chip Gradient Generation", Analytical Chemistry, vol. 76, No. 13, May 2004, pp. 3756-3763.

First Examiner Report received for Australian Application No. 2010284216 mailed Mar. 20, 2014, 5 pages.

(56)

References Cited

OTHER PUBLICATIONS

Examiner Report received for Japanese Application No. 2011-508709 mailed Mar. 4, 2014, 5 pages (3 pages of English Translation and 2 pages of Office Action).
 Examination Report received for Chinese Patent Application No. 200980126549.2 mailed Apr. 28, 2014, 3 pages.
 Examination Report received for Chinese Patent Application No. 201080046911.8 mailed May 6, 2014, 8 pages.
 Examination Report received for Chinese Patent Application No. 201180030341.8 mailed Jul. 2, 2014, 7 pages.
 Examination Report received for Japanese Patent Application No. 2012-525667 mailed on Jun. 6, 2014, 9 pages (5 pages of English Translation and 4 pages).
 Examination Report received for Mexican Patent Application No. MX/a/2010/012213 mailed Apr. 16, 2014.
 Examination Report received for Mexican Patent Application No. MX/a/2013/013831 mailed on Mar. 26, 2014, 1 page.
 International Application No. PCT/US2012/065874, International Preliminary Report on Patentability mailed May 30, 2014, 7 pages.
 International Application No. PCT/US2012/065874, International Search Report and Written Opinion mailed Aug. 7, 2013, 13 pages.

International Application No. PCT/US2013/061443, International Search Report mailed on Jan. 21, 2014, 3 pages.
 International Application No. PCT/US2013/061494, International Search Report and Written Opinion mailed May 28, 2014, 21 pages.
 Notice of Allowance received for Chinese Patent Application No. 200980126549.2, mailed on Aug. 6, 2014, 4 pages (2 pages of original and 2 pages of English translation).
 Examination Report Received for Chinese Patent Application No. 201080046911.8 mailed on Dec. 3, 2014, 6 pages (In accordance with 37 CFR § 1.98(a) (3)).
 Examination Report Received for Mexican Patent Application No. MX/a/2012/002063 mailed on Feb. 27, 2015.
 Examination Report Received for Mexican Patent Application No. MX/a/2010/012213 mailed on Jan. 5, 2015.
 PCT International Patent Application No. PCT/US2010/045897, International Preliminary Report on Patentability mailed Mar. 1, 2012, 9 pages.
 PCT International Patent Application No. PCT/US2011/033329, International Preliminary Report on Patentability mailed Nov. 1, 2012, 13 pages.

* cited by examiner

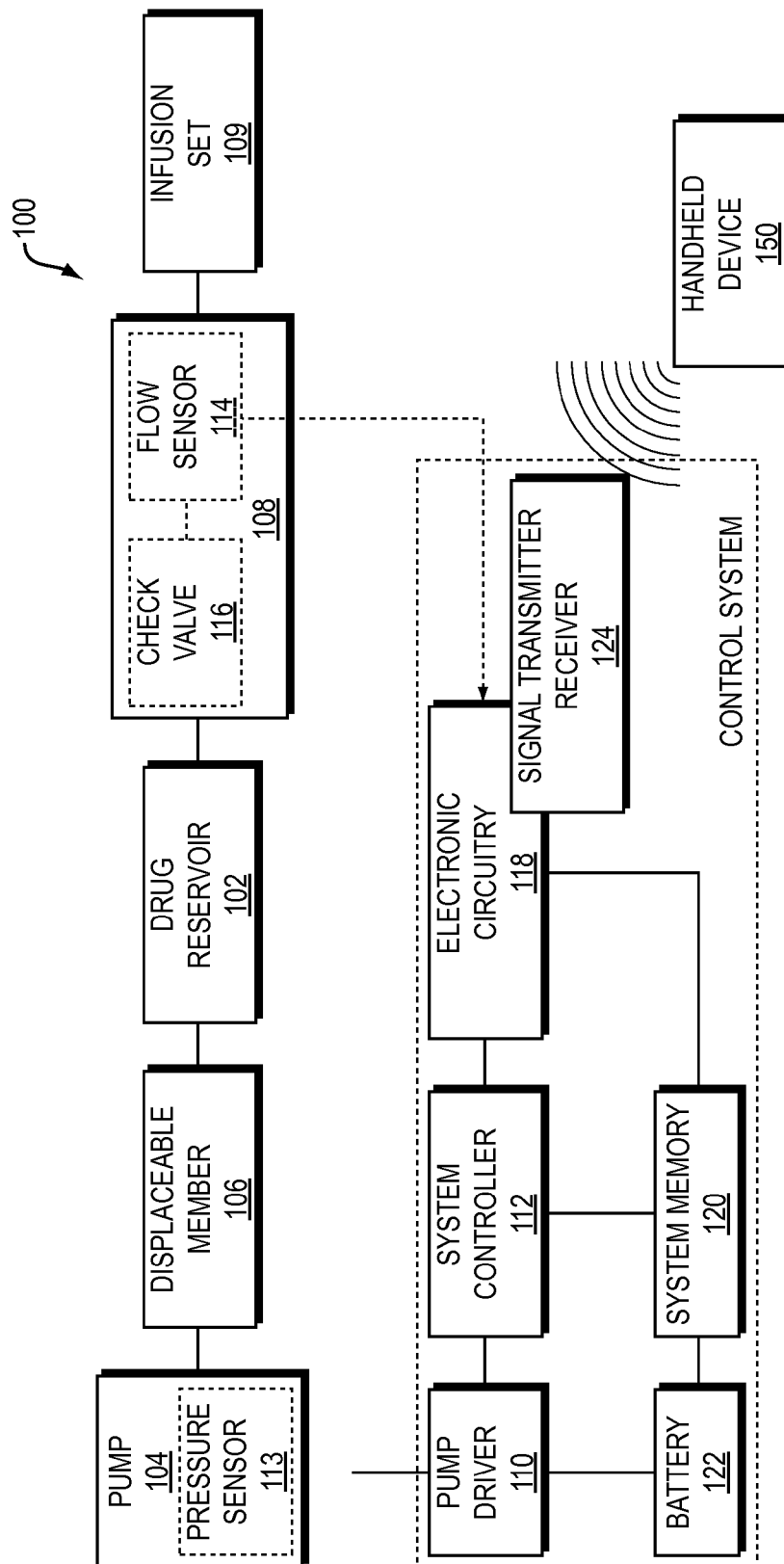


FIG. 1

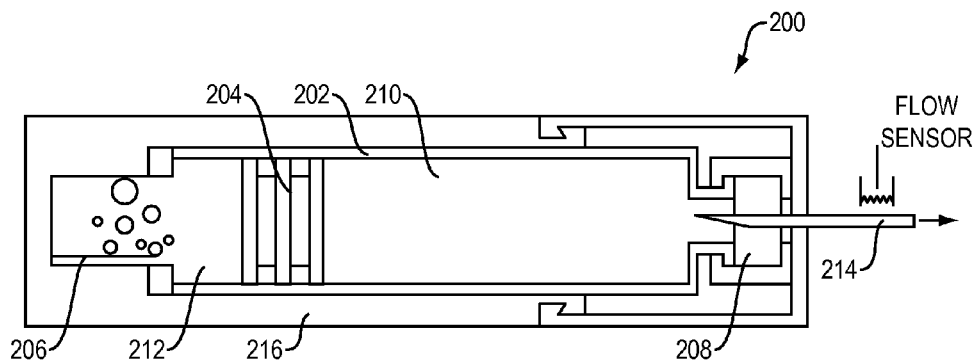


FIG. 2A

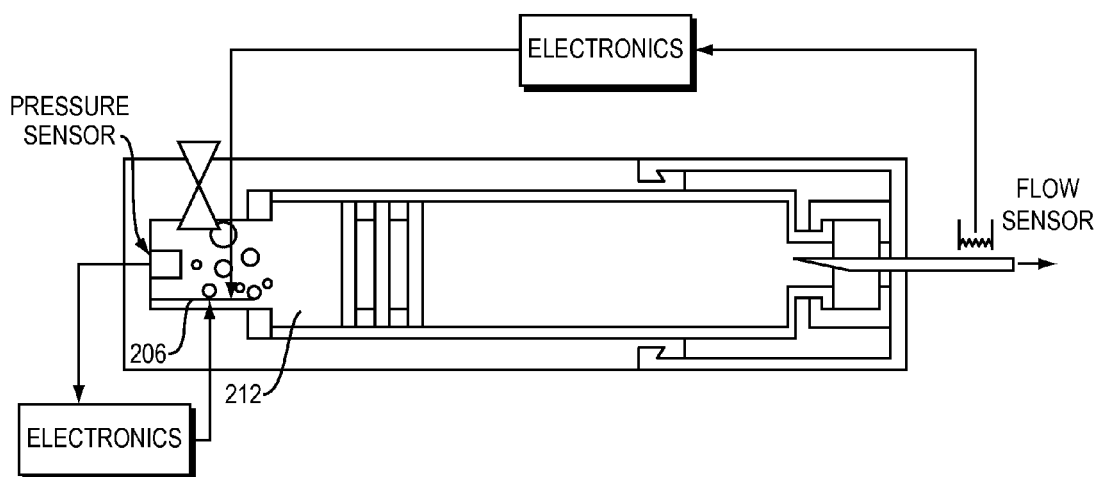


FIG. 2B

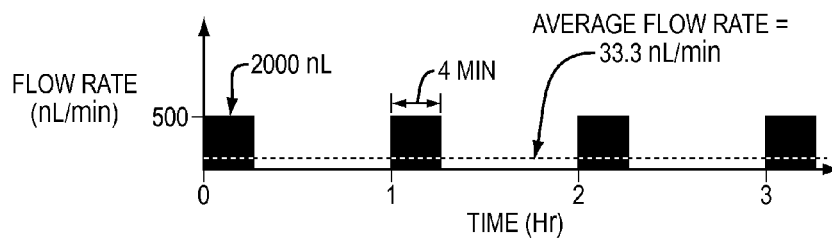


FIG. 3

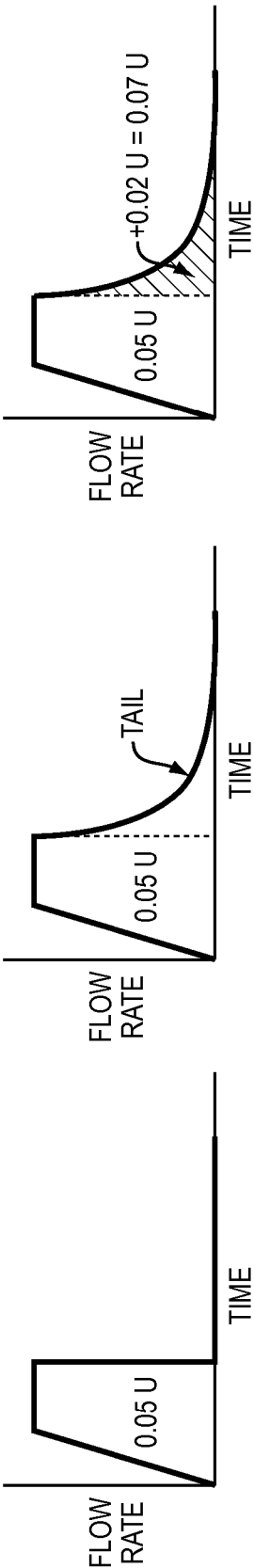


FIG. 4C

FIG. 4B

FIG. 4A

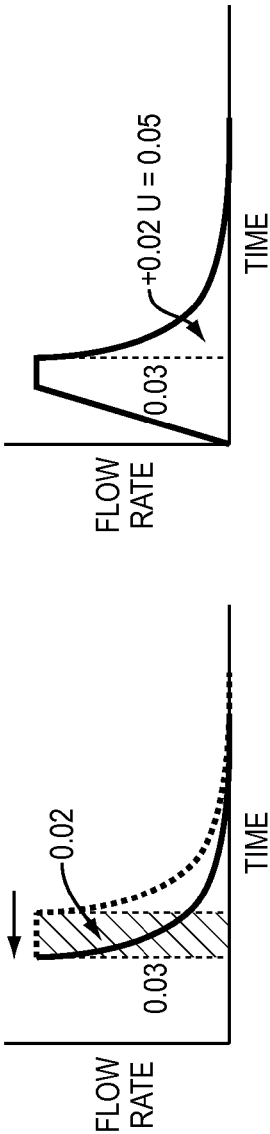
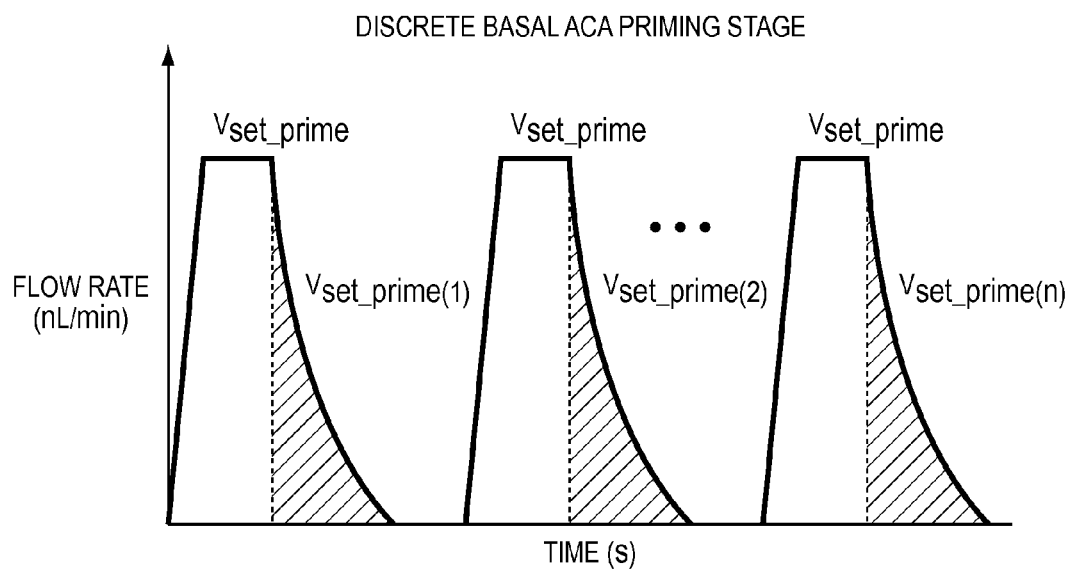
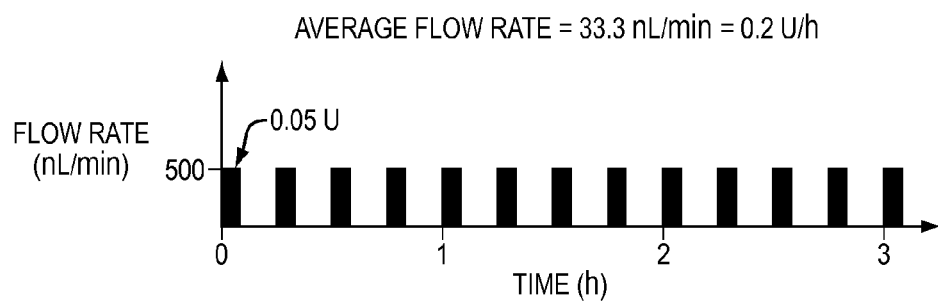
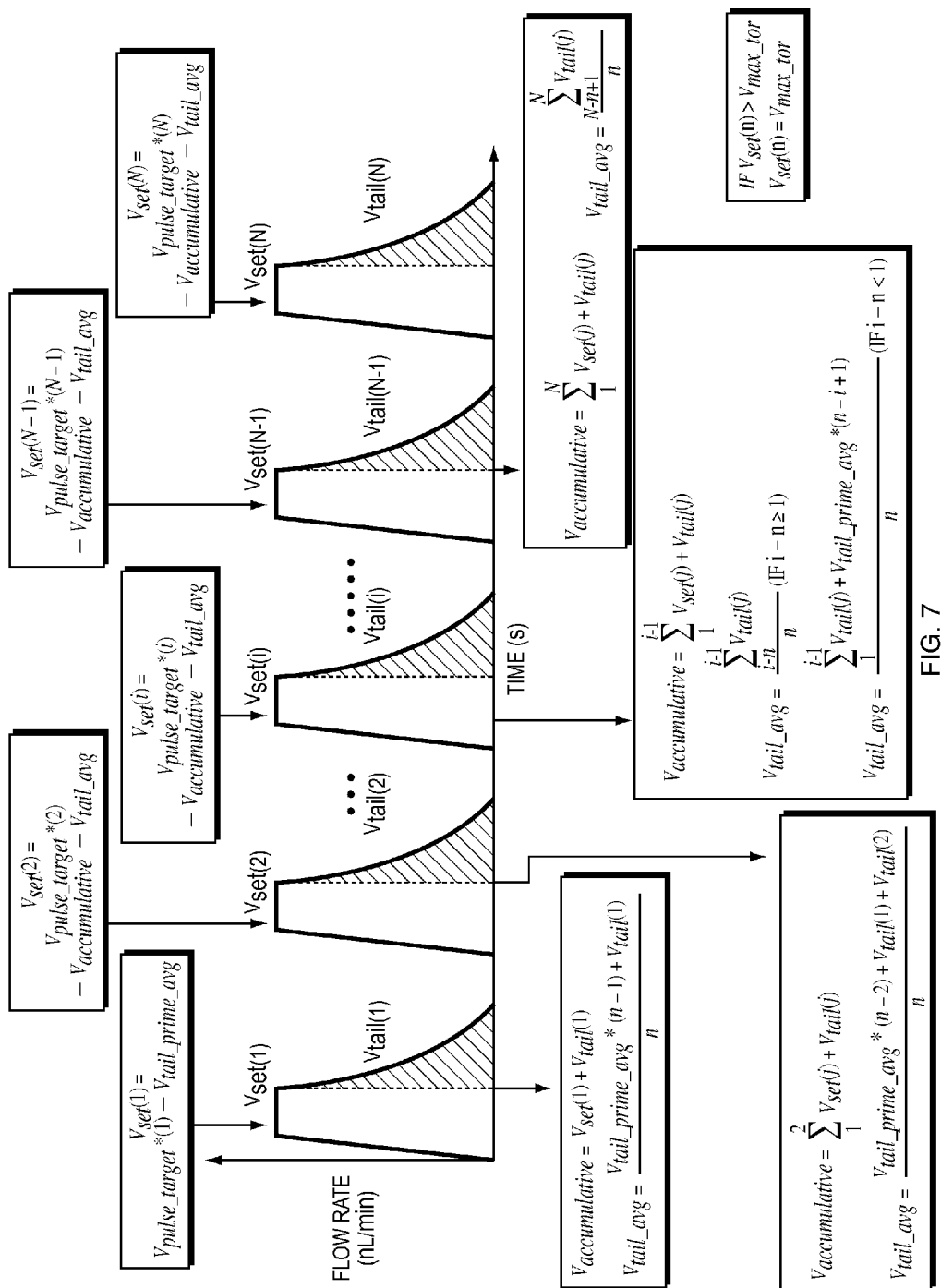


FIG. 4E

FIG. 4D



$$V_{tail_prime_avg} = \frac{\sum_{n=1}^{N_i} V_{tail_prime(n)}}{N_p}$$



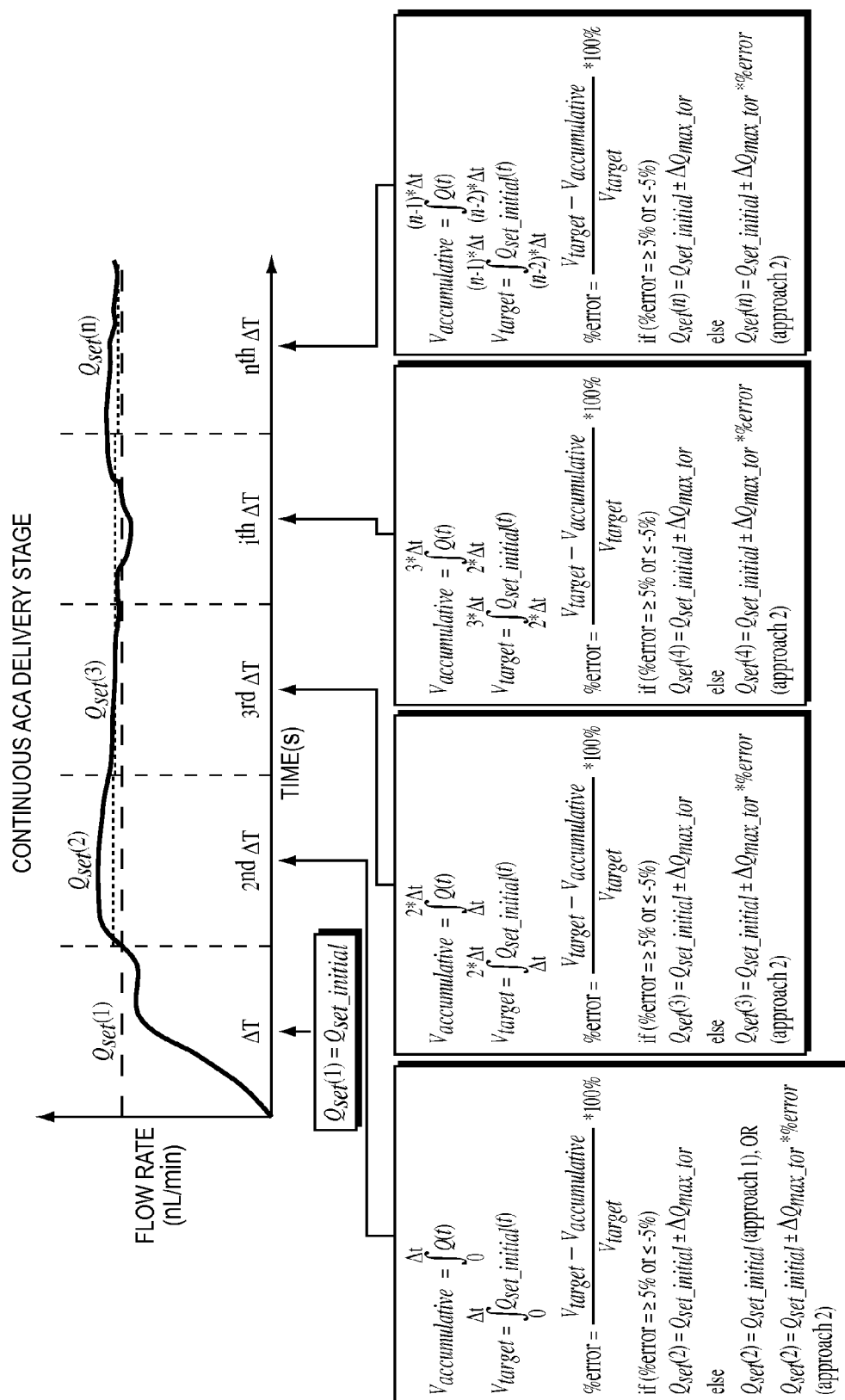


FIG. 8

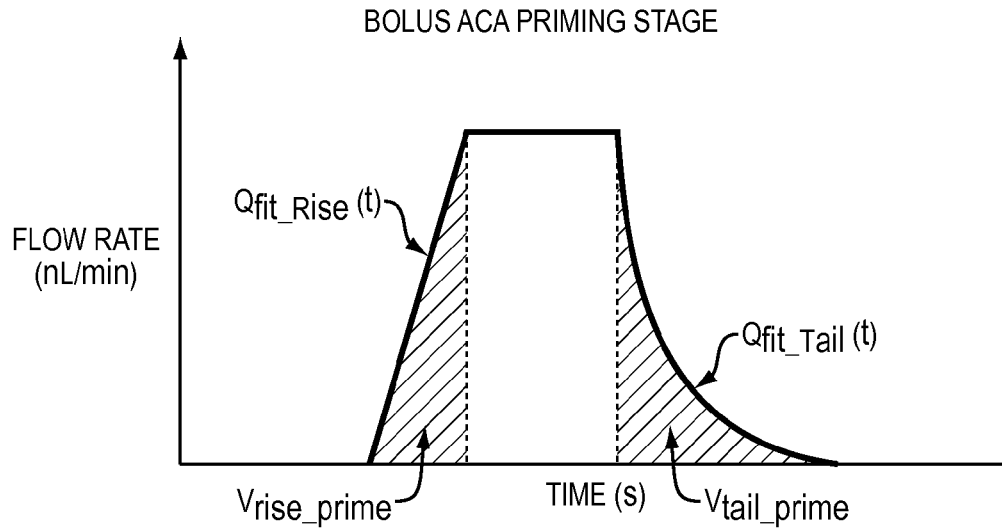
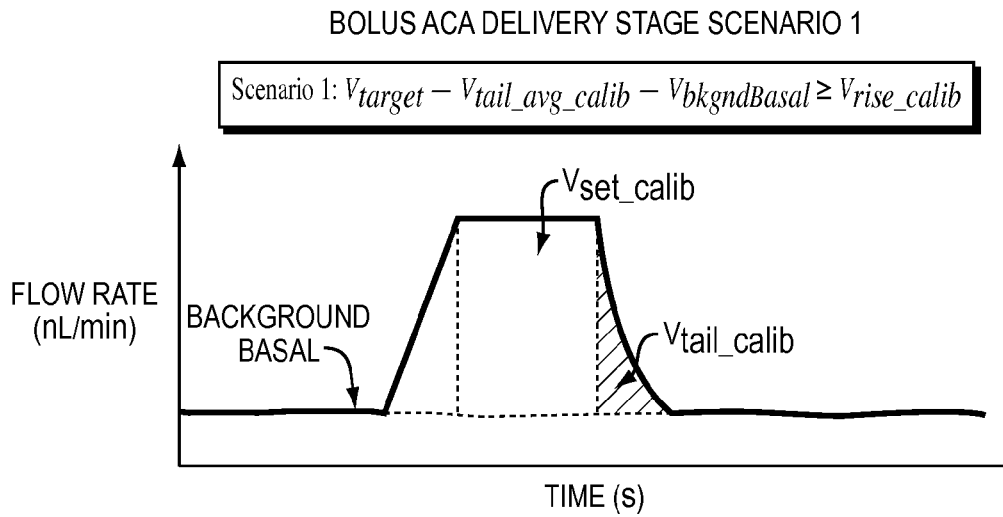


FIG. 9



$$V_{tail_avg_calib} = \frac{\sum_{i=1}^n V_{tail_calib}(i)}{n}$$

$$V_{set_calib} = V_{target} - V_{tail_avg_calib} - V_{bkgndBasal}$$

$$V_{total} = V_{set_calib} + V_{tail_calib}$$

FIG. 10A

1

**DRUG-DELIVERY PUMP WITH
INTELLIGENT CONTROL****CROSS-REFERENCE TO RELATED
APPLICATIONS**

This is a continuation-in-part of U.S. Ser. No. 12/858,808, filed on Aug. 18, 2010, and also claims priority to, and the benefits of, U.S. Ser. No. 61/704,946, filed on Sep. 24, 2012; the entire disclosures of these applications are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to drug-delivery devices, and in particular to control of piston- or plunger-driven drug-pump devices for accurate dosing.

BACKGROUND

Subcutaneous drug delivery is employed for treatment of conditions such as diabetes, and typically involves modalities such as syringe injections, pre-filled pen injectors and patient-filled portable insulin pumps. Pre-filled pen injectors provide accurate manual insulin dosing using, for example, a pre-filled, bubble-free glass cartridge. Since the glass cartridges are bubble-free, the priming process is simple for the patient. Since the injection is performed manually, however, patient compliance is a challenge; the patient may not observe proper injection timing and/or fail to follow the dosing prescription. Portable insulin pumps can provide fully controlled insulin delivery, improving patient compliance, and reduced numbers of injections (once every 3 days, for example) and programmable dosing schedules enhance the patient's quality of life. Patch pumps with low pump profiles can be attached to the patient's skin without interfering with daily activities such as including showering, sleeping, and exercising. Because these pumps are typically filled by patients, however, risks arise during the priming procedure. Improperly primed reservoirs may contain large air bubbles and cause the pump to inject too much air into the subcutaneous tissue, which poses serious safety concerns.

Accordingly, portable pumps with small footprints and pre-filled drug reservoirs can address various problems including those discussed above. One of the challenges for pumps utilizing glass vials as drug reservoirs is to provide controlled and accurate drug delivery. This challenge arises due to varying stiction/friction forces between the surface of the plunger and glass vial. Even under the same driving pressure, these variable forces may cause the drug to be delivered at different flow rates for basal (continuous) delivery. It will also make bolus delivery (i.e., delivery of a discrete dose over a short time period) unpredictable from one bolus to the next.

A related problem observed in connection with piston-driven pumps is a characteristic residual "tailing" of the flow rate—that is, if the amount of fluid expelled is plotted as a function of time, the plot will contain an asymmetric peak having a steepened front portion and an extended tail portion. This is evident, for example, in many drug-delivery devices that contain a drug reservoir formed of compliant materials. This tailing effect leads to a longer delivery time and, once again, inaccuracies in delivery volume.

SUMMARY

Embodiments of the present invention utilize a closed-loop feedback control system to ensure accurate drug delivery.

2

This control system may, for example, utilize a flow sensor to measure the volume of delivery and an intelligent control algorithm to anticipate and compensate for overdoses and underdoses. Feedback control systems in accordance herewith can be applied to any piston- or plunger-driven pump system (hereafter, collectively, "driven" pumps) utilizing sensors that measure flow directly or indirectly. An advantage to this approach is adaptation of the control algorithm to the pump's output, ultimately resulting in extremely accurate drug delivery.

In general overview, a driven pump device in accordance herewith typically includes a cylindrical vial or cartridge with an outlet, and a piston or plunger movable therein. The piston/plunger divides the interior of the vial into a front chamber that is filled with liquid drug and, thus, forms the drug reservoir, and a back chamber that contains the pump mechanism that drives the piston. For example, in electrolytic drug pump devices, the back chamber, or "pump chamber," may contain a pair of electrodes and an electrolyte from which, upon application of a drive current to the electrodes, electrolysis gas evolves, building up pressure in the chamber that pushes the piston forward so as to expel drug through the outlet. Other pump mechanisms (e.g., osmotic, electrochemical, motor-driven, etc.) may also be used.

In general, the drug flow rate of a piston pump device can be regulated via the drive force/pressure applied by the pump; for electrolytically driven pump devices, for example, this is, in turn, a function of the drive current. The pump can be operated continuously to dispense drug at a desired steady flow rate, or in a "pulsed" manner (i.e., turning the pump on and off at certain intervals for specific periods of time) to deliver a series of discrete drug volumes. (Which mode of operation is used often depends on the drug regimen. For instance, diabetes patients usually need a continuous, low "basal" rate of insulin, in addition to high-rate, short-duration "bolus" deliveries before or after meals.) Sometimes, frequent small-volume bolus injections are used to provide, on average, a very low basal rate; this is called "discrete basal delivery." As explained above, the actual mechanics of piston pump devices can undermine the accuracy of drug delivery. One problem is the variable stiction/friction between the piston and glass vial, which can cause unstable flow rates despite constant drive pressure. Another problem is the compression of the piston (which is usually made of a rubber-like material) during pump operation, which results, after the pump has been turned off, in a residual "tail" of drug flow as the piston relaxes from its compressed state. This tail can be strongly affected, in addition, by fluid viscosity, which can vary with the particular drug composition as well as the temperature at administration. As a result of this tail, the actual drug volume delivered is larger than the "set" volume, which is the set flow rate during pump operation multiplied by the time period of operation.

Embodiments of the present invention address these inaccuracies by measuring the flow rate of drug (with any suitable flow-rate sensor disposed at the drug reservoir outlet or in a cannula, needle, or other fluid conduct downstream thereof) and adjusting pump operation based thereon in real time. For bolus deliveries, the "tail volume" (i.e., the volume of liquid delivered during the residual tail described above) may be measured during a priming stage (before drug is injected into the patient), and the "set volume" decreased such that the sum of tail volume and set volume equals the desired dosage. Similarly, for discrete basal delivery, the set volume for each pulse is adjusted based on the average tail volume of a number of immediately preceding pulses. For "continuous basal delivery" (or simply "continuous delivery"), in which fluid is

dispensed continuously rather than in discrete pulses, the accumulated delivered volume may be repeatedly measured for a time window, and deviations of the measured volume from the target volume (i.e., the target flow rate times the length of the time window) are compensated for by adjusting the set flow rate for the next time window (typically between upper and lower flow-rate boundaries).

Accordingly, in a first aspect, the invention relates to a drug pump device. In various embodiments, the device comprises a drug reservoir; an exit member for fluidically connecting the reservoir with a drug injection site; a sensor; an electrolysis pump comprising a pump chamber in mechanical communication with the drug reservoir via an intervening displacement member, where the electrolysis pump is operable to exert a pressure to drive the displacement member toward the exit member and thereby force therethrough fluid in the drug chamber; and control circuitry for (i) storing a target delivered volume over a specified time, (ii) operating the electrolysis pump to force fluid from the drug reservoir into the exit member in pulses having a time window defined by a pump-start time when pumping begins and a pump-stop time when the pump is shut off, the time window corresponding to the target delivered volume at a predetermined flow rate, (iii) based on signals received from the sensor, measuring a volume of fluid through the exit member resulting from a pulse, the measured volume including a pulse volume through the exit member during the pulse and an additional tail volume through the exit member after the pulse, and (iv) adjusting the pulse time window based on the measured pulse volume and tail volume to conform collectively to the target delivered volume. In various embodiments, the sensor is at least one pressure sensor. In other embodiments, the sensor is at least one flow sensor, and in still other embodiments the sensor comprises or consists of at least one flow sensor and at least one pressure sensor.

The target delivered volume may correspond to a single bolus, in which case the control circuitry may cause measuring to occur during a priming stage and causing adjustment to occur during a delivery stage. Alternatively, the control circuitry may be configured to cause the target delivered volume to be dispensed through the exit member over a sequence of time-separated pulses occurring over a time interval; in these implementations, the control circuitry causes measuring to occur during a first time interval and causing adjustment to occur during a second time interval following the first time interval. In some embodiments, adjustment is based on the measured pulse volume and tail volume from a plurality of pulses.

In another aspect, the invention relates to a method of controlling an actual delivery volume of fluid to conform to a target delivery volume in a drug pump device comprising a drug reservoir, an exit member for fluidically connecting the reservoir with a drug injection site, and an electrolysis pump operable to force fluid from the drug reservoir into the exit member in pulses each having a time window defined by a pump-start time when pumping begins and a pump-stop time when the pump is shut off. The time window corresponds to a target delivered volume at a predetermined flow rate. In various embodiments, the method comprises measuring a volume of fluid through the exit member resulting from a pulse, where the measured volume includes (i) a pulse volume through the exit member during the pulse and (ii) an additional tail volume through the exit member after the pulse; and adjusting the pulse time window based on the measured pulse volume and tail volume to conform collectively to the target delivered volume. The measurement may be made with at least one pressure sensor and/or at least one flow sensor. In

some embodiments the target delivered volume corresponds to a single bolus, in which case the measuring step occurs during a priming stage and the adjusting step occurs during a delivery stage. In other embodiments the target delivered volume is dispensed through the exit member over a sequence of time-separated pulses occurring over a time interval, in which case the measuring step occurs during a first time interval and the adjusting step occurs during a second time interval following the first time interval. Moreover, the adjusting step may be based on the measured pulse volume and tail volume from a plurality of pulses.

These and other objects, along with advantages and features of the present invention herein disclosed, will become more apparent through reference to the following description, the accompanying drawings, and the claims. Furthermore, it is to be understood that the features of the various embodiments described herein are not mutually exclusive and can exist in various combinations and permutations. As used herein, the term “substantially” means $\pm 10\%$ and, in some embodiments, $\pm 5\%$. A “measure” or “measurement” may be direct or indirect, i.e., a value derived from a directly measured value.

DESCRIPTION OF THE DRAWINGS

In the drawings, like reference characters generally refer to the same parts throughout the different views. Also, the drawings are not necessarily to scale, with an emphasis instead generally being placed upon illustrating the principles of the invention. In the following description, various embodiments of the present invention are described with reference to the following drawings, in which:

FIG. 1 is a block diagram illustrating the various functional components of electrolytic drug pump devices in accordance with various embodiments;

FIGS. 2A and 2B are schematic side views of piston pump devices in accordance with various embodiments;

FIG. 3 illustrates how repeated, alternating pulses and non-delivery periods can be combined to obtain an averaged flow rate equal to a targeted flow;

FIGS. 4A-4E graphically depict operation of an adaptive control algorithm for overcoming a flow “tail”;

FIG. 5, like FIG. 3, illustrates an example of discrete basal delivery achieved by multiple pulse/time deliveries;

FIG. 6 graphically depicts computation and use of average tail volumes in a compensating flow scheme at the priming stage;

FIG. 7 graphically depicts computation and use of average tail volumes in a compensating flow scheme at the delivery stage;

FIG. 8 graphically depicts the operation of an adaptive control algorithm for continuous basal delivery;

FIG. 9 graphically depicts the operation of an adaptive control algorithm for bolus delivery at the priming stage; and

FIG. 10A graphically depicts the delivery stage of the bolus algorithm; and

FIG. 10B graphically depicts the delivery stage of the bolus algorithm in a situation where the bolus volume is small and the peak flow rate never reaches the maximum dosing rate.

DETAILED DESCRIPTION

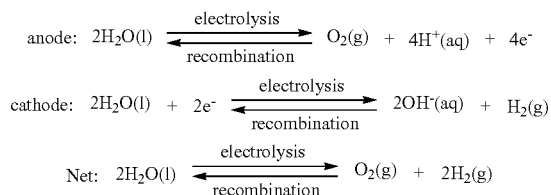
1. Pump Architecture

FIG. 1 illustrates, in block diagram form, the main functional components of a drug pump device 100 in accordance with various embodiments of the present invention. In general, the pump device 100 includes a drug reservoir 102 that

5

interfaces with an electrolysis pump **104** via a displaceable member **106**. The displaceable member **106** may be, for example, a piston, diaphragm, bladder, or plunger. In use, the drug reservoir **102** is filled with medication in liquid form, and pressure generated by the pump **104** moves or expands the displaceable member **106** so as to push the liquid drug out of the reservoir **102**. A cannula, needle, or other exit member **108** connected to an outlet of the drug reservoir **102** conducts the liquid to an infusion set **109**. The infusion set **109** may include a catheter fluidically connected to the cannula **108** for delivering the drug to a subcutaneous tissue region. A lancet and associated insertion mechanism may be used to drive the catheter through the skin. Alternatively, the infusion set **109** may include another type of drug-delivery vehicle, e.g., a sponge or other means facilitating drug absorption through the skin surface.

The electrolysis pump **104** generally includes an electrolyte-containing chamber (hereinafter also referred to as the “pump chamber”) and, disposed in the chamber, one or more pairs of electrodes that are driven by a direct-current power source to break the electrolyte into gaseous products. Suitable electrolytes include water and aqueous solutions of salts, acids, or alkali, as well as non-aqueous ionic solutions. The electrolysis of water is summarized in the following chemical reactions:



The net result of these reactions is the production of oxygen and hydrogen gas, which causes an overall volume expansion of the drug chamber contents. Gas evolution occurs even in a pressurized environment (reportedly at pressures of up to 200 MPa, corresponding to about 30,000 psi). As an alternative (or in addition) to water, ethanol may be used as an electrolyte, resulting in the evolution of carbon dioxide and hydrogen gas. Ethanol electrolysis is advantageous due to its greater efficiency and, consequently, lower power consumption, compared with water electrolysis. Electrolysis pumps in accordance with several embodiments are described in detail further below.

The pressure generated by the drug pump **104** may be regulated via a pump driver **110** by a system controller **112** (e.g., a microcontroller). The controller **112** may set the drive current and thereby control the rate of electrolysis, which, in turn, determines the pressure. In particular, the amount of gas generated is proportional to the drive current integrated over time, and can be calculated using Faraday’s law of electrolysis. For example, creating two hydrogen and one oxygen molecule from water requires four electrons; thus, the amount (measured in moles) of gas generated by electrolysis of water equals the total electrical charge (i.e., current times time), multiplied by a factor of $\frac{3}{4}$ (because three molecules are generated per four electrons), divided by Faraday’s constant.

The system controller **112** may execute a drug-delivery protocol programmed into the drug pump device **100**, and may be responsive to one or more sensors **113**, **114** that measure an operational parameter of the device **100**, such as the pressure in the pump chamber **104** or the flow rate through (or pressure in) the cannula **108**. For example, the controller

6

112 may adjust the current supplied to the electrolysis electrodes based on the pressure inside the pump chamber to achieve a target pressure. The target pressure, in turn, may be calculated based on a desired flow rate, using a known relationship between flow rate and pressure (as determined, e.g., by calibration). Due to the low cost of pressure sensors (such as, e.g., MEMS sensors as used in the automotive industry), this option is particularly advantageous for pumps designed for quick drug delivery. Indeed, two or more pressure sensors **113** may be placed in the pump chamber to simultaneously monitor pressure therein; this redundancy provides additional feedback to the controller **112**, improves accuracy of information, and serves as a backup in case of malfunction of one of the sensors. Alternatively, the rate of drug flow out of the reservoir **102** may be measured directly and in real-time, using a flow sensor **114** integrated in the exit member **108** in a conventional manner. The total delivered dose can be computed by integrating the flow rate over time, and may serve as a control parameter for the electrolysis current as described in greater detail below.

In some embodiments, a pressure sensor **113** inside the pump chamber is used in combination with a flow sensor **114** in the cannula to increase the accuracy and precision of the feedback control loop. The use of multiple sensors also ensures that, in case the flow sensor **114** fails, the pressure sensor **113** would be able to detect high drug delivery rates, and shut the pump **104** down to avoid administration of an overdose to the patient or damage to the pump device. Conversely, the combination of flow and pressure sensors **114**, **113** can also detect a violation in the drug reservoir **102** if pressure is measured in the pump chamber but no flow is measured in the cannula **108**, indicating a potential leak. In general, the sensors used to measure various pump parameters may be flow, thermal, time of flight, pressure, or other sensors known in the art, and may be fabricated (at least in part) from parylene—a biocompatible, thin-film polymer. The cannula **108** may also include a check valve **116** that prevents accidental drug delivery and backflow of liquid into the drug reservoir **112**; like the sensor **114**, the check valve **116** may be made of parylene. In other embodiments, silicon or glass are used in part for the flow sensor **114** and valve **116** construction.

The drug pump device **100** may include electronic circuitry **118** (which may, but need not, be integrated with the system controller **112**) for conditioning and further processing the sensor signal(s) and, optionally, providing pump status information to a user by means of LEDs, other visual displays, vibrational signals, or audio signals. In addition to controlling the drug pump **104**, the controller **112** may be used to control other components of the drug pump system; for example, it may trigger insertion of the lancet and catheter. The system controller **112** may be a microcontroller, i.e., an integrated circuit including a processor core, memory (e.g., in the form of flash memory, read-only memory (ROM), and/or random-access memory (RAM)), and input/output ports. The memory may store firmware that directs operation of the drug pump device. In addition, the device may include read-write system memory **120**. In certain alternative embodiments, the system controller **112** is a general-purpose microprocessor that communicates with the system memory **120**. The system memory **120** (or memory that is part of a microcontroller) may store a drug-delivery protocol in the form of instructions executable by the controller **112**, which may be loaded into the memory at the time of manufacturing, or at a later time by data transfer from a hard drive, flash drive, or other storage device, e.g., via a USB, Ethernet, or firewire port. In alternative embodiments,

the system controller **112** comprises analog circuitry designed to perform the intended function.

The pump driver **110**, system controller **112**, and electronic circuitry **118** may be powered, via suitable battery electronics, by a battery **122**. Suitable batteries **122** include non-rechargeable lithium batteries approximating the size of batteries used in wristwatches, as well as rechargeable Li-ion, lithium polymer, thin-film (e.g., Li-PON), nickel-metal-hydrate, and nickel cadmium batteries. Other devices for powering the drug pump device **100**, such as a capacitor, solar cell or motion-generated energy systems, may be used either in place of the battery **122** or supplementing a smaller battery. This can be useful in cases where the patient needs to keep the drug-delivery device **100** on for several days or more.

In certain embodiments, the drug pump device **100** includes, as part of the electronic circuitry **118** or as a separate component, a signal receiver **124** (for uni-directional telemetry) or a transmitter/receiver **124** (for bi-directional telemetry) that allows the device to be controlled and/or re-programmed remotely by a wireless handheld device **150**, such as a customized remote control or a smartphone. In certain embodiments, the handheld device **150** and pump device **100** communicate over a (uni- or bidirectional) infrared (IR) link, which may utilize one or more inexpensive IR light-emitting diodes and phototransistors as transmitters and receivers, respectively. Communication between the drug pump device **100** and the handheld device **150** may also occur at radio frequencies (RF), using, e.g., a copper coil antenna as the transmitter/receiver component **124**.

The drug-delivery device **100** may be manually activated, e.g., toggled on and off, by means of a switch integrated into the pump housing. In some embodiments, using the toggle switch or another mechanical release mechanism, the patient may cause a needle to pierce the enclosure of the drug reservoir **102** (e.g., the septum of a drug vial, as explained below with respect to FIGS. 2A and 2B) to establish a fluidic connection between the reservoir **102** and the cannula **108**; priming of the pump can then begin. During priming, liquid is pumped from the reservoir through the fluid path, ideally displacing air with liquid up to the tip of the injection needle. Coupling insertion of the needle into the reservoir **102** with the activation of the pump device ensures the integrity of the reservoir **102**, and thus protects the drug, up to the time when the drug is injected; this is particularly important for pre-filled drug pump devices. Similarly, the lancet and catheter of the infusion set **109** may be inserted by manually releasing a mechanical insertion mechanism. In some embodiments, insertion of the lancet and catheter automatically triggers electronic activation of a pump, e.g., by closing an electronic circuit. Alternatively, the pump and/or insertion set may be activated remotely by wireless commands.

The functional components of drug pump devices as described above may be packaged and configured in various ways. In certain preferred embodiments, the drug pump device is integrated into a patch adherable to the patient's skin. Suitable adhesive patches are generally fabricated from a flexible material that conforms to the contours of the patient's body and attaches via an adhesive on the backside surface that contacts a patient's skin. The adhesive may be any material suitable and safe for application to and removal from human skin. Many versions of such adhesives are known in the art, although utilizing an adhesive with gel-like properties may afford a patient particularly advantageous comfort and flexibility. The adhesive may be covered with a removable layer to preclude premature adhesion prior to the intended application. As with commonly available bandages, the removable layer preferably does not reduce the adhesion

properties of the adhesive when removed. In some embodiments, the drug pump device is of a shape and size suitable for implantation.

The various components of the drug pump device may be held within a housing mounted on the skin patch. The device may either be fully self-contained, or, if implemented as discrete, intercommunicating modules, reside within a spatial envelope that is wholly within (i.e., which does not extend beyond in any direction) the perimeter of the patch. The housing may provide mechanical integrity and protection of the components of the drug pump device **100**, and prevent disruption of the pump's operation from changes in the external environment (such as pressure changes). The control system components **110**, **112**, **118**, **120**, **122** may be mounted on a circuit board, which may be flexible and/or may be an integral part of the pump housing. In some embodiments, the control system components are integrated with the electrolysis electrodes into self-contained unit.

Drug pump devices **100** in accordance herewith may be designed for single or repeated use. Multi-use pumps generally include a one-way check valve and a flow sensor, as described above, in the cannula. Further, the drug reservoir of a multi-use pump may be refillable via a refill port, using, e.g., a standard syringe. In some embodiments, the drug pump device **100** is removed from the patient's skin for re-filling. The patient may, for example, place the drug pump device **100** and cartridge containing the new drug into a home refill system, where the pump device and cartridge may be aligned using, e.g., a press-machine mechanism. The patient may then press a button to trigger automatic insertion of a needle that draws liquid drug from the cartridge to the cannula in order to activate the electronics and begin priming the pump.

The electrolysis pump **104** and drug reservoir **102** may be arranged within the device **100** in different ways, the two most common being a piston-pump configuration, in which the pump chamber and reservoir are formed within an elongated vial and separated by a piston movable along the axis of the vial, and the diaphragm-pump configuration, in which the reservoir is disposed on top of the pump chamber and separated therefrom by a flexible diaphragm. Both configurations are described in detail in U.S. patent application Ser. No. 13/091,047, filed on Apr. 20, 2011, which is hereby incorporated herein by reference in its entirety.

FIG. 2A schematically illustrates an exemplary piston pump device **200**. The pump device **200** includes a cylindrical (or, more generally, tubular) vial **202** with a piston **204** movably positioned therein and an electrolysis electrode structure **206** mounted to one end. A septum **208** may be disposed at the other end to seal the vial **202**. Both the piston **204** and the septum **208** may be made of an elastomeric polymer material, such as a synthetic or natural rubber; in some embodiments, silicone rubber (i.e., polydiorganosiloxane, e.g., polydimethylsiloxane) is used. The piston **204** separates the interior of the vial **202** into a drug reservoir **210** and a pump chamber **212**. In use, a needle **214** pierces the septum **208** to allow fluid egress from the drug reservoir **210**; a cannula (not shown) connected to the needle **214** may conduct the fluid to the infusion set (not shown). The piston pump device **200** is enclosed in a protective housing **216**, e.g., made of a hard plastic.

The electrodes **206** may be made of any suitable metal, such as, for example, platinum, titanium, gold, or copper, and may form a pair of parallel wires or plates. Alternatively, to improve electrolysis efficiency, the electrodes can have non-traditional shapes. For example, they may be interdigitated, or individually wound up into a spiral configuration (and oriented so as to face each other). Further, the electrodes **206**

may be embedded in a hydrophilic absorbent material (e.g., a cotton ball) that ensures continuous contact with the electrolyte. This solves a problem frequently encountered with conventional electrolysis pumps, in which the electrodes are simply submerged in liquid electrolyte: as gaseous electrolysis products are generated, they push the piston towards the outlet end of the drug reservoir, thereby increasing the volume of the electrolysis chamber, which causes a decrease in the level of the electrolyte. Depending on the orientation of the device, one or both electrodes may, as a result, gradually emerge from the electrolyte and become surrounded by the gas, eventually forming an open circuit and, thus, causing the electrolysis reaction to cease. This problem can be avoided in various ways, one of which is to surround the electrodes with a hydrophilic absorbent material such as (but not limited to) a hydrogel, cotton ball, sponge, or super-absorbent polymer. The electrolyte stays inside the hydrophilic absorbent material, which efficiently expels the generated gas and keeps the electrodes replenished with electrolyte.

The vial **202** may be fabricated from a glass, polymer, or other materials that are inert with respect to the stability of the drug and, preferably, biocompatible. Polymer vials, e.g., made of polypropylene or parylene, may be suitable for certain drugs that degrade faster when in contact with glass, such as protein drugs. For many other drugs, glass is the preferred material. Glass is commonly used in commercially available and FDA-approved drug vials and containers from many different manufacturers. As a result, there are well-established and approved procedures for aseptically filling and storing drugs in glass containers, which may accelerate the approval process for drug pump devices that protect the drug in a glass container, and avoid the need to rebuild a costly aseptic filling manufacturing line. Using glass for the reservoir further allows the drug to be in contact with similar materials during shipping. Suitable glass materials for the vial may be selected based on the chemical resistance and stability as well as the shatterproof properties of the material. For example, to reduce the risk of container breakage, type-II or type-III soda-lime glasses or type-I borosilicate materials may be used.

To enhance chemical resistance and maintain the stability of enclosed drug preparations, the interior surface of the vial may have a specialized coating. Examples of such coatings include chemically bonded, invisible, ultrathin layers of silicon dioxide or medical-grade silicone emulsions. In addition to protecting the chemical integrity of the enclosed drugs, coatings such as silicone emulsions may provide for lower and more uniform friction between the piston and vial.

In certain embodiments, the piston pump device **200** is manufactured by fitting a conventional, commercially available glass or polymer drug vial, which may already be validated for aseptic filling, with the piston **204** and electrolysis pump components. A screw-in needle cassette may be placed over the septum **208**, and a mechanical actuation mechanism may serve to screw the cassette into the vial **202** such that the cassette needle **214** punctures the septum **208** and establishes a connection with the cannula at the time the patient desires to use the pump. To accommodate the electrolysis pump, the vial **202** is, in some embodiments, longer than typical commercially available vials, but maintains all other properties such that validated filling methods and the parameters of existing aseptic filling lines need not be changed. The drug pump device may be furnished with a prefilled vial. If a glass vial is used, the drugs can be stored in the pump device for long-term shelf life without the need to change the labeling on the drug.

FIG. 2B illustrates the pump **200** with a pressure sensor located in the pump chamber **212**. Signals from the flow

sensor and the pressure sensor are received by programmable circuitry and may be used to regulate pump operation as described in detail below.

2. Feedback Control

Closed-loop feedback control in accordance herewith ensures accurate drug delivery in driven pumps. In one delivery scheme, a pump system delivers drug in discrete doses or pulses, resulting in flow rates that are much lower than the continuous delivery capabilities of the pump. Due to the effect of the stiction of the plunger and glass wall of the cartridge at such a low flow rate, each small discrete dose of drug is generated after the plunger is pushed to overcome the stiction force. Each discrete delivery may overshoot to a flow rate higher than a targeted flow rate, followed by an abrupt stop of the plunger movement causing the flow rate to cease for certain interval. Combining these repeated, alternating pulses and non-delivery periods results in an averaged flow rate theoretically equal to the targeted flow rate and the amount of dose volume equal to the volume obtained from continuous delivery mode. This approach is illustrated in FIG. 3, which shows a discrete dose mode in which the peak flow rate for each pulse is 500 nL/min, the duration for each pulse is 4 min, and the average flow rate representing a continuous constant delivery mode is 33.3 nL/min.

The mechanics of actually delivering these discrete doses, however, can result in inaccuracy (such as an overdose or underdose relative to the desired target delivery). When electrolysis occurs in an electrolytically driven plunger pump, pressure builds up behind the plunger, causing it to compress. When electrolysis stops, however, the plunger relaxes from this compressed state. The relaxation of the plunger material continues to push fluid out of the drug reservoir, causing a prolonged "tail" of the flow rate. This residual flow eventually ceases after the plunger returns to its natural state. The flow sensor enables the system to determine the actual dose delivered, triggering a control algorithm (such as an artificial neural network, fuzzy logic, etc.) that accounts for deviations from the target dose. In other embodiments, a pressure sensor in the pump chamber is used instead of, or in addition to, the flow sensor, since pressure readings are readily correlated with the volume of fluid expelled from the reservoir.

FIGS. 4A-4E illustrate the general concept of an adaptive control algorithm suitable for addressing this problem. In particular, FIG. 4A shows an ideal discrete dose of 0.05 U (which deviates from a perfectly rectangular pulse due to a necessary ramp-up time, which represents proper pump operation and does not vary significantly); FIG. 4B shows the actual delivered dose with additional volume "tail"; FIG. 4C illustrates measurement of the tail at 0.02 U, which totals 0.07 U delivered; the pump stops delivery early at 0.03 U, which accounts for the unwanted tail of 0.02 U shown in FIG. 4D (i.e., the pulse is adjusted so that the tail volume becomes part of the intended delivery volume rather than a deviation therefrom); and FIG. 4E illustrates performance in accordance with embodiments of the present invention, which results in a delivered dose that more accurately tracks the target dose shown in FIG. 4A.

A typical insulin pump should be able to provide bolus and background basal delivery rates over a wide range in order to serve different patients' needs. A prefilled insulin pump in accordance herewith can successfully provide suitable basal and bolus ranges. However, due to the nature of prefilled cartridge pumps, in particular the varying friction between the rubber plunger and glass wall among different cartridges, delivery accuracies can be compromised if corrections for such variation are not made. Thus, a real-time intelligent

control algorithm may be used to compensate for the variation and maintain a very accurate dosage for both basal and bolus delivery.

Due to the unpredictable interaction between the plunger and glass cartridge of a driven pump, many variables can contribute to dosing inaccuracies. Since an initial stiction (initial static friction) exists between the plunger and glass vial, the pump must achieve a minimum pressure before the plunger can move smoothly to deliver a truly continuous flow rate. In this situation, only dynamic friction occurs between plunger and the glass container. On the other hand, the initial stiction (or static friction) may limit the minimum flow rate that the pump can offer and make it very difficult to deliver small amount of drug. To deliver at flow rates below this threshold, a discrete delivery scheme herein termed “discrete basal delivery” may be utilized. In this scheme, the target flow rate is converted to a target volume delivery in a given time period. Several small pulses of insulin are delivered throughout the given time span to achieve the target volume delivery, which fulfills the targeted average flow rate as described in the following equation.

$$\text{Flow Rate } \left(\frac{U}{Hr} \right) = \frac{\text{Total Delivery Volume } (U)}{\text{Time } (Hr)} \quad (3)$$

In one representative embodiment, the the volume of the tail is measured from the previous few (e.g., three) doses the average is determined. The system controller 112 then adjusts the target volume for the next dose based on this average. The following equations may be used by the controller to determine the proper correction.

$$V_{Tail_Avg} = \frac{\sum_{k=0}^n V_{Tail}(k)}{n} \quad (1)$$

$$V_{set}(n) = V_{target}(n) - V_{Tail_Avg} \quad (2)$$

where V_{Tail_Avg} is the average tail volume, V_{Tail} is the individual tail volume, V_{set} is the predicted volume to be delivered excluding the tail volume, and V_{target} is the total expected volume.

A similar approach may be used for continuous delivery. In particular, after analyzing the pump's previous average delivery during a given time period, the system controller 112 adjusts the overall flow rate (on a pulse-by-pulse basis) to correct for the previous delivery error during the next time period.

FIG. 5 illustrates an example of discrete basal delivery achieved by multiple pulse/time deliveries. As shown, there are four bolus deliveries in an hour and the equivalent flow rate is 33.3 nL/min. To generate these small pulses, the pressure in the electrolysis chamber is quickly released at the end of each pulse to accurately obtain the targeted volume for each small pulse. If the pressure is not promptly released, the high pressure will prevent the pump flow from stopping and result in a large over-delivery. Meanwhile, due to residual pressure induced from the plunger/glass interaction and the compliance of the plunger, a “tail” is produced that degrades the accuracy of basal delivery.

In one embodiment that corrects for these errors, the system controller 112 executes an adaptive control algorithm (ACA) during a priming stage and during a delivery stage. At the priming stage, a number n of predetermined pulses (e.g.,

0.05 U/pulse) is scheduled every t minutes. After reaching the target volume for each pulse, the pressure is released and the tail volumes measured. Throughout the priming stage, the system controller 112 (see FIG. 1) collects these tail volumes from a number N_p of pulses to determine an average tail volume. This averaged volume is taken into account in adjusting the time width of the subsequent pulse during the delivery stage. The priming tails are averaged and stored as $V_{tail_prime_avg}$ for future usage. This is illustrated in FIG. 6, in which N_p is the number of discrete basal pulses to be delivered during the priming stage, $V_{tail_prime}(n)$ corresponds to the n^{th} tail volume generated by the n^{th} pulse in the priming stage, and $V_{tail_prime_avg}$ corresponds to the average tail volume of the discrete pulses in the priming stage.

At the delivery stage, as illustrated in FIG. 7, the discrete basal target volume is adjusted according to the average volume of the previous n tails. The first discrete basal pulse, Set Volume or $V_{set}(n)$, is established as follows. After the tail volumes from the n pulses during the priming stage are averaged, $V_{tail_prime_avg}$ is subtracted from V_{target} (the original target volume of the pulse) to give $V_{set}(1)$ (i.e., the adjusted volume for the pulse). In FIG. 7, V_{pulse_target} is the target volume to be delivered in each pulse, $V_{tail}(n)$ is the tail volume produced by each pulse, $V_{cumulative}$ is the actual cumulative volume delivered over time, and V_{tail_avg} is the average tail of the previous n discrete basal pulses.

For each subsequent discrete basal pulse, the system uses the previous n tail volumes in calculating the average tail volume to be used in determining the V_{set} for the current discrete basal pulse. For example, if there are three discrete pulses delivered during the priming stage ($n=3$), V_{tail_avg} for the first pulse in the delivery stage corresponds to the average of these three previous tails, which in this case is the average of these three tail volumes during the priming stage. Next, the value of V_{tail_avg} for the second pulse in the delivery stage corresponds to the average of the three previous tails. However, the three previous tails are the second and third discrete basal pulses in the priming stage and the first pulse of the delivery stage. V_{tail_avg} for the third pulse in the delivery stage corresponds to the average of the third tail in the priming stage and the first and second tails of the delivery stage, and so forth.

A special case arises when V_{set} is negative. This means that there is an overdose from a previous delivery such that the next scheduled pulse should deliver a negative volume to achieve the desired target volume, $V_{target_overall}$. Of course, drug pumps ordinarily cannot operate to withdraw fluid from the patient. Instead, the system sets V_{set} to 0, which causes the controller 112 to skip the pulse in an effort to correct for a previous over-delivery and achieve the correct overall target volume, $V_{target_overall}$. Also, to reduce any over-delivery caused by missing multiple pulses, the system can set a maximum tolerance volume to be delivered at each pulse (V_{max_tor}). The V_{set} volume never exceeds V_{max_tor} . If it does, the system controller 112 will coerce V_{set} to be equal to V_{max_tor} . This ensures overall profile stability, and also ensures the absence of dramatic change in overdose and underdose caused by frequent over-delivery and missed pulses.

It should be noted that the tail volume can vary over the lifetime of the pump or even during an operating cycle based on various factors. Accordingly, calibration is typically performed periodically rather than, for example, a single time when the pump is first used. For example, the response of an electrolysis-driven pump to a given input current supplied to the electrolysis electrodes depends on how much liquid is remaining in the drug reservoir and the gas/liquid ratio in the

electrolysis chamber. Other factors can cause the response of the pump to change over time including, for example, degradation of electrolysis electrodes, changes in the concentration of the electrolyte in the electrolysis chamber, changes in the flow characteristics of valves in the fluid path, and restrictions that form at the exit port due to tissue growth or some other mechanism.

Similar to discrete basal delivery, continuous basal delivery faces challenges due to the plunger and glass-wall friction. Ordinarily it is not necessary to deliver a pulse pattern in continuous basal delivery (as contrasted with discrete basal delivery), and during continuous pumping, the plunger operates above its stiction range. Nonetheless, a continuous adaptive control algorithm can increase the accuracy of drug delivery by minimizing the errors caused by interaction between the plunger and the glass wall.

In one embodiment, a continuous adaptive control routine continuously monitors the accumulated volume and its deviation from the target volume. The routine sets a time window, ΔT , and maximum tolerable flow rate range, ΔQ_{max_tor} . The routine calculates the actual volume delivered during ΔT and its deviation from the target volume. Based on the deviation, a target flow rate, $Q_{set}(2)$, for the next ΔT window is determined in order to compensate for the error in delivery during the first ΔT window. The maximum tolerance, ΔQ_{max_tor} , comes into play when there is too much error in delivery during the first ΔT and $Q_{set}(2)$ has been raised or decreased beyond the physiological range from $Q_{set_initial}$. In such case, $Q_{set}(2)$ is coerced to equal $Q_{set_initial} \pm \Delta Q_{max_tor}$ depending on the delivery error during previous sampling time. This process repeats throughout continuous basal delivery to ensure the overall stability of the flow profile and delivery accuracy.

There are many ways to raise the Q_{set} for the next ΔT time window. A simple example is to have only three possible values for Q_{set} : $Q_{set_initial}$, $Q_{set_initial} + \Delta Q_{max_tor}$, and $Q_{set_min} - \Delta Q_{max_tor}$. In one embodiment, if the cumulative delivered volume did not deviate from the cumulative target volume by more than an acceptable percentage (e.g., 5%) at the end of the sampling period ΔT , then the system will set Q_{set} to $Q_{set_initial}$, which is the initial flow-rate set point. If the actual delivered volume exceeds the target volume by more than the acceptable percentage (e.g., 5%), Q_{set} is set to $Q_{set} + \Delta Q_{max_tor}$ for the next time window ΔT . If the actual delivered volume falls below the target volume by more than the acceptable percentage (e.g., 5%), Q_{set} is set to $Q_{set} - \Delta Q_{max_tor}$ for the next time window ΔT .

In another embodiment, illustrated in FIG. 8, a continuous spectrum of $Q_{set}(n)$ values is used. In the figure, ΔT is a predefined time window, $Q_{set}(n)$ is the target flow rate during the time window, $Q_{set_initial}$ is the initial target flow rate (which is also equal to Q_{set} , the overall target flow rate), $V_{cumulative}$ is the actual cumulative volume delivered over time, and V_{target} is the target cumulative volume over time, % error represents the error percentage (i.e., the deviation from V_{target}) by volume, and ΔQ_{max_tor} is the maximum flow rate that Q_{set} cannot exceed.

Each $Q_{set}(n)$ value inversely corresponds to a percentage deviation above or below the target delivery volume from the previous sampling period. If the cumulative delivered volume exceeds the cumulative target volume by more than an acceptable percentage (% error), $Q_{set}(n)$ is set to $Q_{set_initial} - \% \text{ error} \times \Delta Q_{max_tor}$ for the next time window ΔT . If the actual delivered volume falls below the target volume by more than % error, $Q_{set}(n)$ is set to $Q_{set_initial} + \% \text{ error} \times \Delta Q_{max_tor}$ for the next time window ΔT . Once again, the $Q_{set}(n)$ can never go below $Q_{set_initial} - \Delta Q_{max_tor}$ or above $Q_{set_initial} + \Delta Q_{max_tor}$

or the system will coerce the $Q_{set}(n)$ to be set at $Q_{set_initial} - \Delta Q_{max_tor}$ or $Q_{set_initial} + \Delta Q_{max_tor}$.

More generally, various algorithms and controllers can be used to adjust pump operation through monitoring and adjustment during time windows. During a time window, for example, a closed-loop control scheme, such as proportional-integral-derivative ("PID") controller, on-off controller, fuzzy logic controller, proportional controller, and/or linear controller can be applied to maintain as constant a target delivery parameter such as flow rate. In the next time window, the constant target delivery parameter can be altered based on the comparison result from the previous time window. For example, a PID controller may be used during a timing interval, while a different algorithm, such as the ACA, may be used between time windows to alter the PID controller settings (e.g., the constant target delivery flow rate, the acceptable upper and lower ranges of flow rates, and constants for positional, integral, and derivative calculations). Accordingly, parameters that can be monitored and adjusted include flow rate, pressure, volume, current, and voltage. Moreover, the integration or differentiation of any one or more of these parameters may be monitored and adjusted.

Bolus delivery faces the same accuracy challenges caused by the tail volume as the discrete basal pulses. However, boluses are delivered on demand, and the accuracy of each individual bolus cannot be compensated by another bolus. In the case of insulin delivery, boluses are usually preceded and followed by a background basal delivery; for example, a bolus may be administered just before mealtime, after which insulin is delivered at the background basal rate until the next bolus. In such applications the bolus adaptive control algorithm can be relatively simple, as it may be based solely on tail volume to achieve overall accuracy. In other scenarios, however, the flow profile may be more complex and/or unpredictable; for example, the rate of drug administration may be varied periodically or continuously based on the monitored value of a physiologic, environmental or blood-borne chemical concentration parameter.

In one embodiment, the real-time bolus adaptive control algorithm involves a priming stage and a delivery stage. During the priming stage, a bolus (e.g., 1 U) is delivered and the tail volume is measured until the flow rate reaches zero. This bolus is sufficient in volume to allow the system to pump the flow rate up to its maximum dosing rate (e.g., 30 U/Hr for insulin pump). If the user selects a smaller bolus volume, the peak bolus flow rate may never reach the maximum dosing rate (e.g., 30 U/Hr). If the user selects a large bolus volume, the peak bolus target flow rate can be kept at the maximum dosing rate (e.g., 30 U/Hr) using a flow-sensor-based closed-loop control system as described, for example, in copending application Ser. No. 13/680,828, filed on Nov. 19, 2012 (the entire disclosure of which is hereby incorporated by reference); it simply takes longer to finish the bolus.

Operation during the priming stage is illustrated in FIG. 9. The white rectangle represents V_{set_prime} , i.e., the desired volume to be delivered. Additional flow during ramp-up (V_{rise_prime}) and during the tail (V_{tail_prime}) is modeled by fitted curves $Q_{fit_Rise}(t)$ (flow rate vs. time during the ramp up stage) and $Q_{fit_Tail}(t)$ (representing the tail after V_{set_prime} has completed). The areas under these fitted curves correspond to V_{rise_prime} (the volume delivered during ramp-up) and V_{tail_prime} (the volume delivered during the tail segment). After obtaining the tail volume information and its curve, interpolation can be used to predict the tail volume for different boluses with different potential peak flow rates. The interpolated curve and the peak flow rate at the end of the bolus can be used to predict the tail volume.

15

Two delivery-stage scenarios are illustrated, respectively, in FIGS. 10A and 10B. In FIG. 10A, the flow pattern corresponds to that shown in FIG. 9, with a peak flow rate is that is substantially constant (flat). A calibrated tail volume $V_{tail_avg_calib}$ is used to calculate the actual delivery bolus volume, which is equal to the difference between the target volume V_{target} and the total predicted tail volume (including the background basal cumulative volume); thus, the calibrated set volume V_{set_calib} is equal to $V_{target} - V_{tail_avg_calib} - V_{BkgndBasal}$. The total bolus volume V_{total} actually delivered is equal to $V_{set_calib} + V_{tail_calib}$, where V_{tail_calib} is the actual run-time tail volume (this time ignoring the background basal cumulative volume).

If the bolus volume is small and the peak flow rate never reaches the maximum dosing rate (e.g., 30 U/Hr) before the target bolus volume has been delivered, a curve-fitting technique may be used to predict the peak flow rate as illustrated in FIG. 10B; here the tail volume is estimated between the predicted peak flow rate and the (actual) background basal flow rate. This can give a very accurate prediction of the tail volume, and during the actual delivery this is used to compensate for the effect of the tail effect. In FIG. 10B, T_0 is the bolus start time; T_{Qpeak} is the time at which the bolus reaches the maximum peak set flow rate Q_{peak} ; ΔT is an adjustment time set to create a fitted curve as shown in FIG. 10B (and may range from, e.g., 1 ms to 1 s depending on the application in order to balance acceptable error and power restrictions that determine the sample rate and, in turn, the duration of the sample time interval); T_1 is the time when $Q_{tail_calib}(t)$ (the fitted tail curve) reaches $Q_{tail_calib} \times (T_{Qpeak} - \Delta T)$; T_2 is the time when $Q_{tail_calib}(t)$ reaches $Q_{tail_calib} \times (T_{Qpeak} - 2\Delta T)$; and $T_{BkgndBasal}$ is the time when $Q_{tail_calib}(t)$ reaches the background basal flow rate.

After delivery is complete, the tail volume is stored in memory along with the estimated (fitted) curve. This historical tail behavior may be used to predict the tail volume for future boluses delivered from the same cartridge.

As discussed above, the priming stage is typically employed to evacuate air from the fluid path of the device, preventing air and/or debris from being injected into the target site, and also wets any sensors in the fluid path. Because of the faults that priming is designed to remediate, calibrating during the priming stage may not be ideal. In some embodiments, therefore, a non-therapeutic dose is dispensed by the pump following priming, and this dose is used instead of or in addition to the priming stage for calibration purposes. For example, it may be necessary to use the non-therapeutic dose for calibration if the sensor used therefor is in the fluid path and must be wet to operate properly. As used herein, the term "non-therapeutic dose" means a volume of drug less than a therapeutic dose, and in some embodiments, a dose small enough to avoid any therapeutic effect or clinically significant effect.

It should be emphasized that, although the preceding discussion has focused on a single target dosage, this need not be the case. Many medications, including monoclonal antibodies, require dosages based on the patient's weight or the severity of the diseases. Accordingly, pumps in accordance herewith may have the ability to deliver a range of target dosages; in some embodiments, a dose-selection mechanism is incorporated—for example, a dose-selection interface may allow the user to select the dosage, which is programmed into memory within the controller 112. This interface may be or include a switch, dial, buttons, touch screen, or a variety of user-interface components. The dosage may also be pre-set by the manufacturer, clinician, pharmacist, or other non-patient entity, and locked for security purposes.

16

Certain embodiments of the present invention were described above. It is, however, expressly noted that the present invention is not limited to those embodiments, but rather the intention is that additions and modifications to what was expressly described herein are also included within the scope of the invention. Moreover, it is to be understood that the features of the various embodiments described herein were not mutually exclusive and can exist in various combinations and permutations, even if such combinations or permutations were not made express herein, without departing from the spirit and scope of the invention. In fact, variations, modifications, and other implementations of what was described herein will occur to those of ordinary skill in the art without departing from the spirit and the scope of the invention. As such, the invention is not to be defined only by the preceding illustrative description.

What is claimed is:

1. A drug pump device comprising:

a drug reservoir;

an exit member for fluidically connecting the reservoir with a drug injection site;

a sensor;

an electrolysis pump comprising a pump chamber in mechanical communication with the drug reservoir via an intervening displacement member, the electrolysis pump being operable to exert a pressure to drive the displacement member toward the exit member and thereby force therethrough fluid in the drug chamber; and

control circuitry for (i) storing a target delivered volume over a specified time, (ii) operating the electrolysis pump to force fluid from the drug reservoir into the exit member in pulses having a time window defined by a pump-start time when pumping begins and a pump-stop time when the pump is shut off, the time window corresponding to the target delivered volume at a predetermined flow rate, (iii) based on signals received from the sensor, measuring a volume of fluid through the exit member resulting from a pulse, the measured volume including a pulse volume through the exit member during the pulse and an additional tail volume through the exit member after the pulse, and (iv) adjusting the pulse time window based on the measured pulse volume and tail volume to conform collectively to the target delivered volume.

2. The device of claim 1, wherein the sensor is at least one pressure sensor.

3. The device of claim 1, wherein the sensor is at least one flow sensor.

4. The device of claim 1, wherein the sensor comprises at least one flow sensor and at least one pressure sensor.

5. The device of claim 1, wherein the target delivered volume corresponds to a single bolus, the control circuitry causing measuring to occur during a priming stage and causing adjustment to occur during a delivery stage.

6. The device of claim 1, wherein the control circuitry causes the target delivered volume to be dispensed through the exit member over a sequence of time-separated pulses occurring over a time interval, the control circuitry causing measuring to occur during a first time interval and causing adjustment to occur during a second time interval following the first time interval.

7. The device of claim 6, wherein the adjustment is based on the measured pulse volume and tail volume from a plurality of pulses.

17

8. The device of claim 1, wherein the intervening displacement member comprises a piston, a diaphragm, a bladder, or a plunger.

9. A method of controlling an actual delivery volume of fluid in a drug pump device comprising a drug reservoir, an exit member for fluidically connecting the reservoir with a drug injection site, and an electrolysis pump operable to force fluid from the drug reservoir into the exit member in pulses each having a time window defined by a pump-start time when pumping begins and a pump-stop time when the pump is shut off, the time window corresponding to a target delivered volume at a predetermined flow rate, to conform to a target delivery volume, the method comprising:

measuring a volume of fluid through the exit member resulting from a pulse, the measured volume including (i) a pulse volume through the exit member during the pulse and (ii) an additional tail volume through the exit member after the pulse; and

adjusting the pulse time window based on the measured pulse volume and tail volume to conform collectively to the target delivered volume.

18

10. The method of claim 9, wherein the measurement is made with at least one pressure sensor.

11. The method of claim 9, wherein the sensor is at least one flow sensor.

12. The method of claim 9, wherein the target delivered volume corresponds to a single bolus, the measuring step occurring during a priming stage and the adjusting step occurring during a delivery stage.

13. The method of claim 9, wherein the target delivered volume is dispensed through the exit member over a sequence of time-separated pulses occurring over a time interval, the measuring step occurring during a first time interval and the adjusting step occurring during a second time interval following the first time interval.

14. The method of claim 13, wherein the adjusting step is based on the measured pulse volume and tail volume from a plurality of pulses.

* * * * *